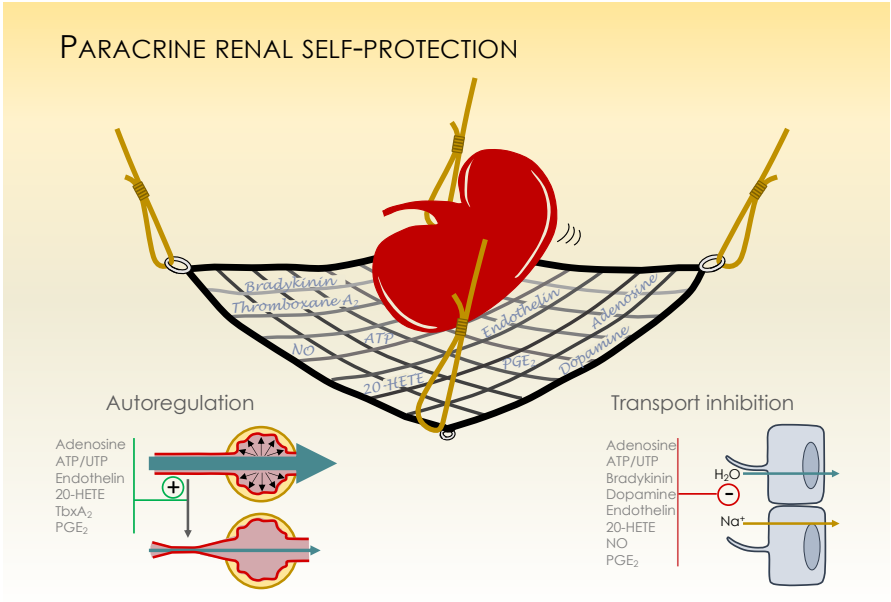
Renal autocrine and paracrine signaling -a story of self-protection

Jens Leipziger[1,2] *and Helle Praetorius*[1]
[1]*Department of Biomedicine, Physiology Aarhus University*
and [2]*Aarhus Institute of Advanced Studies (AIAS), Aarhus University*

Abstract

Autocrine and paracrine signaling in the kidney adds an extra level of diversity and complexity to renal physiology. The extensive scientific production on the topic precludes easy understanding of the fundamental purpose of the vast number of molecules and systems that influence the renal function. This systematic review provides the broader pen strokes for a collected image of renal paracrine signaling. First, we recapitulate the essence of each paracrine system one by one. Thereafter the single components are merged into an overarching physiological concept. The presented survey shows that despite the diversity in the web of paracrine factors, the collected effect on renal function may not be complicated after all. In essence, paracrine activation provides an intelligent system that perceives minor perturbations and reacts with a coordinated and integrated tissue response that relieves the workload from the renal epithelia and favors diuresis and natriuresis. We suggest that the overall function of paracrine signaling is reno-protection and argue that renal paracrine signaling and self-regulation are two sides of the same coin. Thus, local paracrine signaling is an intrinsic function of the kidney, and the overall renal effect of changes in blood pressure, volume load, and systemic hormones will always be tinted by its paracrine status.



Call out

We are born with a finite number of functioning nephrons that steadily declines with advancing age. The rate of decline is accelerated by various lifestyle risk factors and chronic diseases. Renal insufficiency is one of the leading challenges for the health systems worldwide, and the capacity for renal transplantation cannot meet the needs. Thus, it is pertinent to defining renal protective factors and regimes that postpone the date for running into renal insufficiency. This review evaluates the kidney's own line of defense. We suggest that the sum of autocrine and paracrine signaling in the kidney, in essence, provides an intelligent system that perceives minor perturbations and reacts with a coordinated and integrated tissue response that relieves the workload from the renal epithelia and favors diuresis and natriuresis. Thus, paracrine signaling provides reno-protection through self-regulation, and constitutes an attractive interventive target.

Correspondence: Helle Praetorius, hp@biomed.au.dk
Department of Biomedicine, Aarhus University
Høegh-Guldbergsgade 10 (Build 1115), 8000 Aarhus C

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1. Introduction

The kidneys are fascinating. Two modest sized, bean-shaped organs that each day produce 150-180 l of pre-urine by filtering our blood and reabsorbing the vast majority leaving only roughly one liter for excretion. Despite this, the kidneys have a moderate regenerative capacity compared to other epithelial organs like the liver, skin, or the intestine, and the nephrons we are born with are not replaceable. Instead of regeneration, the kidney meets highly variable demands with a solid repertoire for self-regulation and self-protection reflected in the numerous systems of local autocrine and paracrine signaling. In classical physiology, the ability of an organ to self-protect has been referred to as autoregulation. The term is commonly used for regulation of the blood flow of a given organ in response to its oxygen demand and in the case of the kidney regulation of the blood flow for a steady filtration over a broad range of systemic blood pressure. This implies that the effect of systemic hormones, exercise, and posture on the systemic blood pressure is stifled by the kidney, which provides a steady renal function and protects the organ against acute and chronic damage. The classic renal autoregulation has been resolved to be one example of efficient local renal paracrine signaling either isolated in the vasculature or between the renal epithelia and the vasculature. Renal autoregulation demonstrates how efficiently local signaling can be in modifying organ function. However, the kidney has a more extensive repertoire of auto/paracrine signaling than the ones involved directly in the classical autoregulation. The question is whether they serve a common purpose.

Per definition, autocrine signaling constitutes a paradigm where a substance released from a given cell activates receptors on the same cell with following downstream signaling, whereas paracrine signaling refers to cell-to-cell signaling between either neighboring cell or cells in closer vicinity (Fig. 1). Discussing autocrine and paracrine signaling in a renal context, one has to bear in mind that the kidney predominantly is an epithelial organ. The main cellular components of the kidney are epithelial, particularly since endothelial cells are a subgroup of epithelia. In addition to the epithelia, the kidney has a smaller fraction of smooth muscle cells, pericytes, interstitial cells, nerve-endings, and various immune cells, which under physiological conditions encompass tissue macrophages. A continuous epithelium works as a syncytium, that is, the adjacent cells respond in a coordinated fashion serving a common purpose. A true syncytium can be provided by gap-junctional connections between the cells as seen between vascular smooth muscle cells, smooth muscle cells/endothelial cells, or even some of the tubular cells.

However, cells need not be directly electrically coupled to show a coordinated response. A tissue response can also be coordinated through communication provided by release substances that synchronize the cell function to a given external stimulus. This essentially means that any of the cells in the epithelium could be the one sensing a given external stimulus and communicating the stimulus to the surrounding cells and that any of the cells also can be the recipient of the local signaling event (Fig. 1). This is an intriguing system that allows the tissue to react to a given stimulus with a coordinated response, rather than a collection of single cells that all individually have to sense an external signal to respond (Fig. 1). Thus, in tissues with a substantial number of similar cells, the boundary between autocrine/paracrine signaling is slightly blurred.

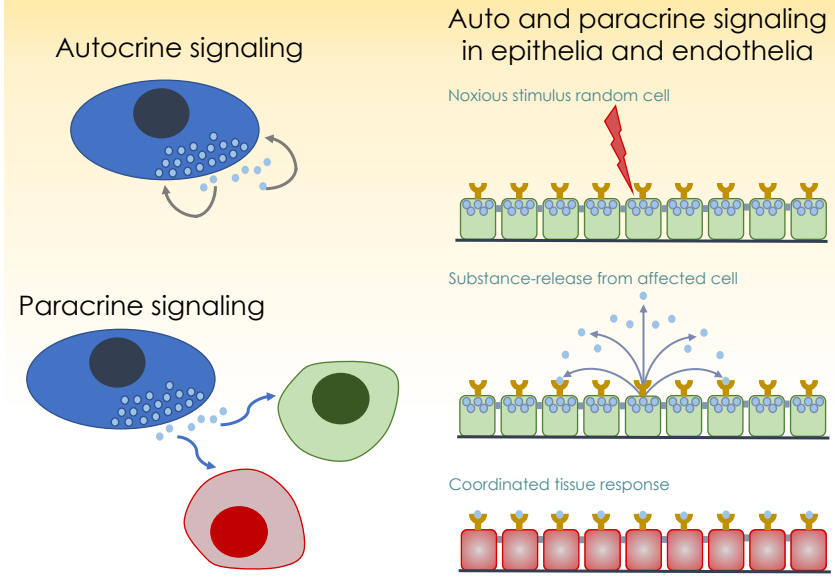

Figure 1- Autocrine and paracrine signaling *The figure illustrates the principle of autocrine and paracrine signaling. The schematics on the left depicter the definitions on autocrine and paracrine signaling. The right part illustrates that the boundaries between the two get blurred in a syncytium of similar cells where it is hard to have autocrine without paracrine signaling.*

Moreover, if the cells are very similar, they would have close to the same pattern of receptor expression. Therefore, it is hard to imagine autocrine signaling without a paracrine component and vice versa. The predicament is thus that one can only be certain of a factor is working in a paracrine manner if the signaling occurs between two distinct cell types, and one can essentially only be sure of autocrine signaling in isolated cells. Therefore, in this review, we only make a distinction between the two where there is firm proof for one or the other.

Despite that local, paracrine signaling is fundamental for a normal renal function, it is not easy to give a simple answer to what the overall implication of paracrine signaling is for the kidney. A browse through the literature reveals a wide fan of suggested paracrine signaling entities to be afoot in the kidney. Strikingly, most effects of the paracrine factors are overlapping, but despite that, only very few studies consider the interaction between the various signaling systems. This review strives to synthesize a new overall concept for the autocrine/paracrine signaling in the kidney. To be able to bridge this enormous topic and argue for an overall principle of renal autocrine/paracrine signaling, conceptual compromises were made. In the review, we limit the interest to the local signaling in physiology, and therefore, local physicochemical factors like urine composition, mechanical stimulation, etc. Thus, it does not include potential nervous stimuli, and we keep a sharp dissociation between systemic effects of the signaling systems and the local effect on renal transport, salt, and water handling. Similarly, the review will not provide an overview of the associated pathology. Moreover, we cannot acknowledge all the interesting work for every single paracrine factor but attempt to sketch the main trends. We ask the following questions to all the proposed signaling systems: 1) is this a true autocrine/paracrine signaling system, 2) what is the overall effect on renal function, and 3) what other paracrine factors does the given factor interact with. Based on this, we will attempt to rank the web of paracrine factors in terms of stimulation, early/later event, and duration for a collective tissue response and propose an overall principle for paracrine signaling in the kidney.

2. Paracrine signaling in the renal vasculature

The kidneys are fascinating organs that service the body's water and salt homeostasis while they excrete potentially toxic substances and retain the substances the body needs. This is performed by an intriguing sequence of extensive filtration of the plasma, with following substantial reabsorption of the essential components. The renal vasculature provides the blood supply necessary for the filtration and for returning the absorbed components to the circulation. The entire filtration process of the kidney relies on the hydrostatic pressure dictated by the relative constriction of the afferent and efferent arteriole and the total renal blood flow. Therefore, it is not surprising that vasoactive components are essential for the overall renal function. Local, paracrine signaling is at the heart of controlling renal function because it is the essence of the renal autoregulation. The renal autoregulation of the blood flow essentially constitutes of (1) the myogenic response in the afferent arteriole and (2) the tubuloglomerular feedback (TGF) mechanism. As illustrated in figure 2, the myogenic response occurs local in the vasculature where the afferent arteriole similar to other arterioles in the body contract in response to acute dilation of the arteriole, and thus, stretching of the vascular smooth muscle cells. The resulting vasoconstriction has clear autocrine/paracrine components that will be examined in more detail below. In contrast, the TGF response is the prime example of communication and interaction between the renal epithelial cells and the vasculature in a clear paracrine fashion. The TGF response allows information about the epithelial transport strain to flow back to the vasculature to readjust the production of pre-urine according to the transport capacity. Interestingly, it is an oversimplification to limit tubular influence on renal blood flow to the TGF. Several studies have implicated interaction between the connecting tubule and the afferent arteriole and interactions between the thick ascending limb and the vasa recta. Therefore, local paracrine tonus is at any given time important for the renal blood flow and the glomerular filtration rate as key determining factors of the overall urinary output. Below, the various autocrine/paracrine regulators are considered for their impact on the overall renal function either as mediators or as modulators of renal autoregulation.

2.1 Nitric oxide, endothelium, and renal blood flow

Nitrogen monoxide (NO) was the first gaseous signaling molecule demonstrated in mammals. It has an overwhelming legacy as a local, paracrine vasodilator (18, 180, 219, 220). This finding was soon recognized as a true paradigm shift and opened up an entire research field, demonstrating the relevance for NO both for normal body function and in pathophysiology. Here we regard the physiological effects, where the classical NO and endothelium-dependent vascular relaxing response is physiologically triggered by a shear stress-dependent increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in the endothelial cells, which in turn activates nitric oxide synthase (NOS) causing NO production and release. In this sense, NO is a true autocrine/paracrine signaling molecule, responding to local stimuli with local short-lasting response. Because the response relies on increased $[Ca^{2+}]_i$ in the endothelial cells, the response can, in principle, be mimicked by any agonist that acting via guanine nucleotide-binding (Gq)-coupled receptors, usually acetylcholine.

The NO-depended vasorelaxation, in response to acetylcholine, has been clearly demonstrated in the renal vasculature (47, 73, 675). Interestingly, some of the referred authors failed to detect any effect of NO-scavenging on the basal perfusion pressure (73), which is consistent with little if any endothelial-derived relaxing factor (EDRF) stimulation during unstimulated, basal conditions. Scavenging NO did, however, completely block the acetylcholine-induced increase in filtration pressure, although a change in artery diameter could not be observed (73). Later, a study by Kaufmann et al. directly demonstrated a concentration-dependent reduction in reno-vascular resistance and an increase in renal plasma flow by NO (310). Moreover, NO release by glomerular endothelial cells has been shown to modify the glomerular microcirculation even at baseline (756). NOS inhibition caused vasoconstriction in both afferent and efferent arteriole. However, since the increase in resistance was found to be more pronounced in efferent arteriole, NOS inhibition also increased in glomerular hydrostatic pressure (120, 756). This effect is presumably a consequence of a cGMP-mediated contraction of the mesangial cells (595).

Generally, capillaries have not been regarded as a site for regulation of tissue perfusion. Newer studies do, however, suggest that the pericytes surrounding the capillary bed in the brain are able to collectively increase and regulate the vascular resistance in a tissue and contribute to the metabolic component of cerebral autoregulation (228). In the kidney, the pericytes surrounding the vasa recta have been proposed to regulate medullary blood flow (481). Apparently, NO signaling not only affects renal arteries and arterioles but also substantially influences medullary microcirculation. The pericytes surrounding the descending vasa recta are interspersed with a distance of 15-20 µm, and in the area of the vasa recta covered by pericytes, NO has been suggested to be a local relaxing factor as shown in both isolated vasa recta (77, 138) and medullary kidney slices (99). The study from Cao et al. primarily addresses the EDRF type response in vasa recta with the endothelium as the NO generating tissue (77). The majority of the mentioned papers that address NO effects on vasa recta have considered adjacent tissues such as the thick ascending limb (TAL) as potential NO donor. The issue of tubular NO generation will be discussed later in section 5.3.

NOS is also known to be expressed in the juxtaglomerular apparatus, and thus, potentially allows local signaling in the kidney to impose systemic effects on the arterial blood pressure. The juxtaglomerular apparatus consists of the macula densa cells interspersed between the thick ascending limb and the distal convoluted tubule, the renin-secreting juxtaglomerular (JG) cells, and the mesangial cells (Fig. 2). This functional unit allows the body to use the kidneys as a sensing organ for the systemic blood pressure. An increase in mean arterial blood pressure will acutely stretch the afferent arteriole and increase the glomerular filtration rate (GFR) and thus, enhance Na^+ and Cl^- delivery to the macula densa cells with the pre-urine. Both of these signals, which are also triggers for renal autoregulation, will reduce renin secretion and consequentially the peripheral production of angiotensin II (AngII) and subsequent release of aldosterone from the adrenals. This, in turn, reduces the contraction of the systemic resistance arterioles and reduces the circulatory volume by increasing renal Na^+ excretion and, thus, collectively, the systemic blood pressure. The salt sensing macula densa cells primarily express nNOS (NOS1), whereas eNOS (NOS3) is mainly found in the corresponding afferent arteriole (671). In this light, one would expect NO signaling to at least modify the renin secretion. Unfortunately, however, the various *in vitro* and *in vivo* studies show variability

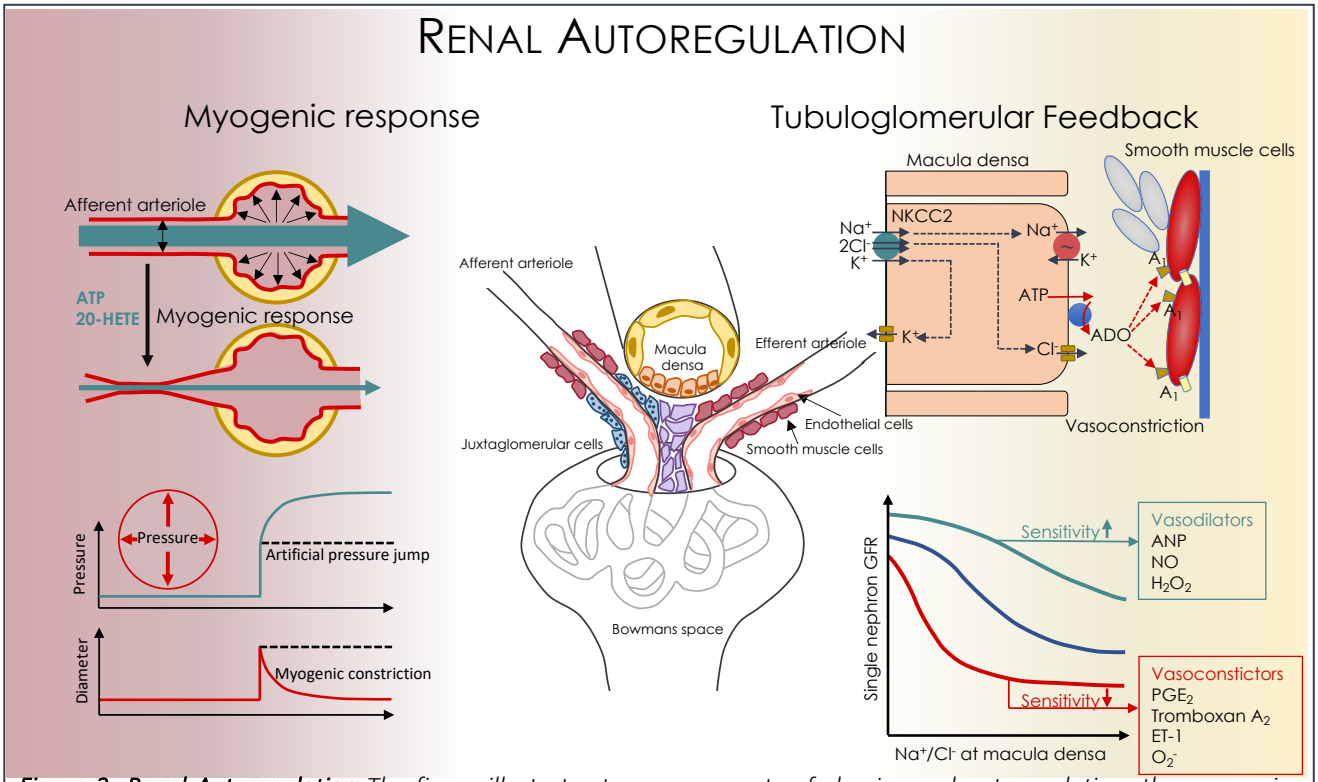

Figure 2- Renal Autoregulation *The figure illustrates two components of classic renal autoregulation; the myogenic response of the afferent arteriole (left panel) and the tubuloglomerular feedback mechanism (right panel). The myogenic response entails the vascular contraction in response to an acute increase in the intravascular pressure. The TGF response entails an interaction from the macula densa cells that sense the intraluminal Na^+ and Cl^- concentration via the transport function of NKCC2 with consecutive adenosine signaling to the smooth muscle cells in the afferent arteriole leasing to contraction.*
Abbreviations: ADO (adenosine), ANP (atrial natriuretic peptide), ATP (adenosin triphosphate), ET-1 (endothelin 1), NKCC2 (Na^+-K^+-$2Cl^-$ cotransporter 2), NO (nitric oxide), PGE_2 (prostaglandin E2).

in the direction of the response. Some of the early studies on kidney slices show that NO/EDRF reduce renin secretion (39, 695). NO-induced inhibition of renin secretion immediately fits with the overall concept for the systemic renin-angiotensin-aldosterone system (RAAS), where elevation of the blood pressure and increased shear stress in afferent arteriole would inflict EDRF resulting in reduced renin release and a subsequent reduction in blood pressure. However, renin has been demonstrated to be released in response to a direct increase in intracellular cAMP (173), and thus, one expects that NO via cGMP would give the same effect. Consistent with this, studies on co-culture of JG/endothelial cells and *in vivo* studies support that NO donors or EDRF increase renin release (38, 583, 597, 660). These data suggest that EDRF and NO signaling in the case of regulation of renin secretion rather function as a feed-forward mechanism that keeps the systemic blood pressure high in a situation with high shear stress in the afferent arteriole. This would underscore that the RAAS system is primarily serving the systemic circulation rather than the kidney.

Other sources for local NO generation: In addition to NO supplied by NOS, apparently NO production can also be supported by other means. Supplementary NO , in principle, be generated from nitrate and nitrite, and it has been speculated that the nitrate and nitrite available through the diet is sufficient to produce a physiological relevant supplement to the NOS-dependent NO production (for overview see (386)). Vegetables are the primary dietary source of nitrate, and nitrate released from the diet components is reduced to nitrite by commensal bacteria already in the oral cavity (132). Moreover, nitrite is commonly added to meat products for conservation, where it reduces growth of *Clostridium botulinum* (for overview see (48)), which on a particular diet may contribute to the available circulating nitrite. A number of enzymes are able to catalyze the reduction of nitrite to NO (for overview see (720)), including carbonic anhydrase (1). The latter is particularly interesting since it can

potentially contribute to adjusting the vascular diameter to the metabolic demand of a given tissue and can be supported by all cells with significant carbonic anhydrase activity. Supplementary dietary nitrate and nitrite have been shown to be able to reduce blood pressure in both normotensive and hypertensive individuals (305, 354, 717). Interestingly, this effect has been ascribed to the microvasculature of the kidney. This is particularly based on the vasodilatory effect of nitrite (10 μM) that completely abolished the vasoconstrictor response to AngII in perfused afferent arterioles, which was not the case in interlobar, carotid or mesenteric arteries (184). This subarea still is in its infancy regarding potential effects in renal physiology. However, if the notion that carbonic anhydrases are central to this pathway is correct, the kidney is then bound to be an exceptionally relevant target tissue because of its extensive expression of CA and its high degree of perfusion with CA-containing erythrocytes.

Non-endothelial NO production sites: Typically, NO is released by the endothelial cells, but in principle, the smooth muscle cells/pericytes will react to any cell type that can release NO as long as the diffusion distance is minimal. As previously mentioned, the renal epithelium has been found to generate NO for cross-talk between TAL and vasa recta (125, 423). NO has also been proposed as a neurotransmitter mediating neurogenic vasodilation (668, 669). This theory has been particularly promoted in cerebral arteries of dogs and monkeys, although it has never been firmly established as one of the cerebral autoregulatory mechanisms (for overview see (648)). Irrespective of the lack of consensus on this subject, the same concept has been suggested for the kidney. In several tissues, including the kidney, NO-dependent vasodilation is only detected during α-adrenergic blockage, which indicates that the sympathetic neurons release both norepinephrine and NO, creating a moderated vasoconstrictor response (670). Interestingly, it has been proposed that renal production of NO by neuronal nitric oxide synthase (nNOS) mainly contributes to adequate perfusion of the renal medulla, and inhibition of nNOS results in some 22 % reduction of the medullary blood flow (702). This is particularly interesting in terms of a possible function of pericytes in the regulation of renal medullary blood flow.

NO, and renal vascular physiology: To what extent does vascular NO signaling influence the overall physiology of the kidney? This question is not easily answered because NO works in a coherent setting of diverse paracrine signaling. Clearly, NO can both be the direct signaling molecule to mechanical changes, but it can also work downstream in signaling cascades that involve increases in $[Ca^{2+}]_i$. Most relevant is the modulatory effect of NO on the renal autoregulation. Here NO as a vasodilatory agent will desensitize the overall myogenic response in the afferent arteriole and the concomitant vasoconstriction mediated via increased Cl^- delivery to the macula densa area (Fig. 2) (580).

2.2 Purinergic signaling in the renal vasculature

The purinergic signaling system is a classic signaling system entailing all the components needed for efficient extracellular signaling: 1) regulated transmitter release, 2) specific receptors for the transmitter, and 3) enzymes for degradation of the transmitter, which allows removal of the signal and re-stimulation of the various receptors. Regarding receptors, the purinergic signaling systems consist of (P1 or A_1, A_{2A}, A_{2B}, and A_3) adenosine receptors, receptors sensitive to ATP, ADP, UTP or UDP (P2 receptors) and as of recent also P0 receptors or adenine receptors. The P2 receptors are further subdivided into metabotropic ($P2Y_{1,2,4,6,11,12,13,14}$) receptors and ionotropic ($P2X_{1-7}$) receptors. Whereas the P2X receptors are primarily activated by ATP, several P2Y receptors are sensitive to UTP ($P2Y_2$/$P2Y_4$), ADP ($P2Y_1$, $P2Y_{12}$), and UDP ($P2Y_6$) either selectively ($P2Y_{12}$/$P2Y_6$) or in addition to ATP ($P2Y_1$/$P2Y_2$/$P2Y_4$). ATP is degraded by ectoATP-ases and alkaline phosphatases. The breakdown is a sequential process, which changes the balance between ATP and its degradation products (749, 772). This is particularly noteworthy because most cells express a pallet of P2 and adenosine receptors – and the net signal will depend on the relative expression of these receptors and the relative activity of the degradation enzymes. As an example, the relative expression of NTPDase1 (CD39) degrading ATP to AMP and NTPDase2 (CG39L1), which hydrolyzes ATP to ADP, are both important for the intravascular thrombotic process. CD39/NTPDase1 is expressed on the luminal membrane of endothelial cells, whereas CD39L1/NTPDase2 is associated with the basolateral surface of the endothelium, the

adventitia of muscularized vessels and microvascular pericytes. NTPDase1 has been shown to reduce thrombocyte aggregation and cerebral infarct size (501). However, after endothelial injury, the exposure of NTPDase2 results in relative accumulation of ADP, which will lead to thrombus formation at the site of injury (590). AMP is, in turn, substrate for the 5'-ectonucleotidase (CD73) generating adenosine, which subsequently activates adenosine receptors. Adenosine is further metabolized to inosine by adenosine deaminase or taken up by cells via nucleoside transporters (749). All the principal elements of the purinergic signaling system are found in the kidney (for review see (25, 281, 320, 513, 540, 585, 594, 688)), and thus, all renal cells are to be regarded as potential targets for purinergic signals. The best understood purinergic signal transduction pathway in the kidney is the signaling of the tubuloglomerular feedback (TGF) mechanism between the sensing epithelial cells of the macula densa and the smooth muscle cells of the afferent arteriole (40, 579). The TGF mechanism will be described in some detail later below under adenosine signaling.

Renal vascular adenosine signaling and tubuloglomerular feedback

Adenosine has a very distinct effect on the vasculature of the kidney compared to other tissues. Adenosine is either released directly as adenosine from cells or as ATP with following degradation, as mentioned above. As noted, adenosine inflicts its cellular action by activation of A_1, A_{2A}, A_{2B}, or A_3 receptors, where A_1 is the predominant receptor in the renal vasculature. Through activation of A_1 receptors, adenosine triggers pronounced vasoconstrictions in the kidney (238, 666). This response is in sharp contrast to vascular beds in other tissues were adenosine instead produces marked vasodilation. In fact, some physiology textbooks mention adenosine as one of the mediators of the metabolic response in tissue autoregulation. In reality, adenosine is not a metabolic factor per se but acts downstream from a fall in PO_2. In skeletal muscle, hypoxia or exercise causes an increase in extracellular ATP concentration (166), which is likely causing a rise in extracellular adenosine. Moreover, hypoxia is known to produce vasodilation via activation of K_{ATP} channels ($K_{IR}6.2$/SUR2B) in coronary arteries (109). This effect is at least partially mediated via A_2 receptor stimulation resulting in activation of the K_{ATP} channels in the vascular smooth muscle cells (41, 325). This, in turn, hyperpolarizes the smooth muscle cells, and vasodilation evidently follows. In the renal vasculature, the adenosine effect is the complete opposite, where it has long been known that adenosine cause vasoconstriction in renal arteries (238, 666). This results from the widespread vascular expression of A_1 receptors, which act either via G_i or G_q to cause a decrease in cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activation or an increase in $[Ca^{2+}]_i$. Despite these general notions, the collected effect of adenosine on renal vasculature, when infused, is not entirely clear-cut. Apparently, upon adenosine infusion, the fall in RBF is only transient, and the renal blood flow to the subcortical regions is markedly suppressed, as demonstrated by an altered single-nephron GFR/GFR ratio (477). Thus, the vasoconstrictor effect of adenosine must occur primarily in the cortical areas, whereas the more medullar regions experience vasodilation in response to adenosine. Physiologically this makes sense because the medullary areas are more prone to experience hypoxia, which, as previously mentioned, increases the adenosine concentration in the tissue. The abovementioned findings have been substantiated by later studies demonstrating that selective A_1 receptor agonists reduce blood flow to both cortical and medullary regions, whereas A_2 receptor agonist increase primarily the medullary blood flow in rats (7). In agreement with these findings, adenosine in low concentration causes constriction of micro-dissected medullary rat vasa recta, whereas higher concentrations cause vasodilation (601). These findings fit the demonstration of mRNA for both the adenosine sensitive A_1 receptor and less sensitive A_{2A} and A_{2B} in these vessels (341). Thus, the renal vasculature can respond both to systemically as locally produced adenosine. Since this review only addresses paracrine signaling, we will consider only the latter. Adenosine signaling in the kidney gives us one of the most beautiful examples of paracrine signaling known, the TGF mechanism. Essentially, TGF allows each nephron of the kidney to tightly regulate the filtration rate to the capacity for salt reabsorption along the same nephron (figure 1). The proximal tubule reabsorbs around 65% of the filtered Na^+ and Cl^- regardless of the flow rate, as determined by the glomerular-tubular balance. A substantial amount of the remaining Na^+ and Cl^- is reabsorbed in thick ascending limb of the loop of Henle. The amount that reaches the macula densa will, as a surrogate measure, reflect the load of pre-urine in the tubular

system. Hence, the faster the urine flow, the larger the fraction of Na^+ and Cl^- escapes the Na^+-K^+-$2Cl^-$-cotransporter (NKCC2)-mediated reabsorption in TAL and therefore arrives at the macula densa (Fig. 2). The macula densa cells sense the tubule composition of Na^+ and Cl^- via the $NKCC2_A$ isoform with contribution of the $NKCC2_B$ isoform (352, 467, 468, 573), where luminal [Cl^-] is the rate-limiting factor (580). A large Na^+ and Cl^- concentration will result in substantial reabsorption of these ions via NKCC2, causing a volume challenge for the macula densa cells (317). This volume increase leads to no-lytic release of ATP that is degraded extracellularly to adenosine via NTPDase1 followed by the 5'-nucleotidase CD73 (642) and the degradation of ATP accounts at least for 50% of the adenosine present in the interstitium (82, 268, 466, 533, 664). Adenosine will then via A_1 receptor activation cause constriction of the afferent arteriole (68, 528) and thereby reduce GFR and the volume of pre-urine challenging the system. These studies illustrate the pivotal role of adenosine in the regulation of arteriole diameter in the kidney and, thus, on the overall renal blood flow.

Together with the myogenic response, TGF is the essence of renal autoregulation. This places the A_1 receptor as the single most critical receptor for the renal vascular tone. Many of the other mentioned vasomodulatory hormones, and paracrine factors are able to modulate the TGF mechanism, as discussed below, Table 1). Interestingly, the predominance of A_1 receptors in the regulatory component of the TGF response is evidently a consequence of the concentration of adenosine in the tissue. Experiments conducted in isolated afferent arterioles clearly demonstrate that A_1 receptors are the predominant receptor in the segment of the afferent arteriole closest to the entrance into the glomerular capillaries (719). The up-stream regions do, however, express A_2 receptors in lower functional abundance only detectable at very high concentrations of adenosine (719). Recently, it has become apparent that A_{2A} receptors are involved in the tonic regulation of the diameter of the efferent arteriole. It was shown that luminal perfusion with an A_{2A} receptor antagonist at low concentration enhanced the TGF response, consistent with the A_{2A} receptor modulating the A_1 receptor-dependent TGF response (78). Streptozotocin-treated rats exhibit a reduced efferent arteriolar response to A_{2A} receptor agonist-induced vasodilation, and thus this mechanism has been proposed to participate in hyperfiltration of the early diabetic kidney (496). The reno-protective effect of adenosine is further emphasized by studies showing that renal overexpression of A_1 receptors protects against the tubular damage otherwise observed in connection with ischemia-reperfusion of the liver (487). Taken together, the TGF response is the prime example highlighting the importance of paracrine signaling, but also illustrating the communication between renal tubules and renal vasculature to finetune the overall renal function.

P2-receptor activation in renal vasculature

There is good evidence that $P2X_1$ receptors are expressed in smooth muscle cells and that they readily respond to application of ATP with contraction in a manner that requires extracellular Ca^{2+}. In fact, purinergic signaling as a principle was first shown as the non-adrenergic, non-cholinergic component of nerve/ smooth muscle preparations (72). In a model of tenia coli, it was demonstrated that ATP was released from the same nerve varicosities that liberate norepinephrine (640). This model of neuronal ATP release and following P2 receptor stimulation on the recipient smooth muscle cells was also shown for the vascular system (72, 204, 617), most likely involving the $P2X_1$ receptor (366). In the vasculature, concomitant ATP release will activate P2X receptors, which provides Ca^{2+} influx, membrane depolarization, and subsequently activation of L-type Ca^{2+} channels, which then amplifies the contraction induced by adrenergic α_1 receptors. The renal vasculature has also been shown to express $P2X_1$ receptors. In perfused rat kidney, it was demonstrated that P2 receptor agonists induced biphasic vasoconstriction, with a rapid transient component and a more sustained one (690). The rapid transient vasoconstriction resulted from $P2X_1$ receptor activation, whereas the sustained was attributed to another P2 receptor (690).

Despite that ATP is known to be released as a paracrine factor during TGF response and that $P2X_1$ receptors are functionally expressed in the afferent arteriole, the physiological mediation of the TGF response is primarily A_1 receptor-mediated. Studies using either non-selective P2 receptor antagonists or $P2X_1$ receptor-deficient mice demonstrate that ATP-driven vasoconstriction of the afferent arteriole only contribute with around 15% of the TGF response (533, 578, 579) This may be because of the fast inactivation and desensitization of $P2X_1$, which often makes it difficult to define the contribution of the $P2X_1$ receptors in freshly isolated tissue. Thus, the effect of $P2X_1$ receptors in the

thrombocyte function can only be demonstrated if the thrombocytes are separated carefully in the presence of extracellular ATP scavenging with apyrase (391, 547). Interestingly, $P2X_1$ receptor expression has been shown to be reduced in spontaneously hypertensive rats (211) with a concomitant reduction in the Ca^{2+} responsiveness of the smooth muscle cells in the afferent arteriole (211). The reduced Ca^{2+} responsiveness not only results from the reduced $P2X_1$ receptor function alone but follows a general reduction of the sarcoplasmatic reticulum Ca^{2+}pump (SERCA) and an increased baseline leak from the ryanodine receptors (211). In the light that the $P2X_1$ receptor-deficient mice have been shown to have a reduced myogenic response (283), these data suggest that the $P2X_1$ receptor is insignificant in the TGF response but potentially essential for the myogenic component of the renal autoregulation (Fig. 2). This notion is partially supported by an earlier study showing that inhibition of purinergic receptors by PPADS counteracts the AngII-induced vasoconstriction of the efferent and afferent arteriole, without affecting the AngII-mediated elevation of the systemic blood pressure (169). It must be noted that the mesangial cells have been demonstrated to express $P2Y_2$ and $P2Y_4$ receptors (234, 421), which are likely to be involved in the $[Ca^{2+}]_i$ increase observed in mesangial cells in response to macula densa dependent sensing of the luminal Cl^- concentration. There is, however, not any reports on P2Y receptors being implicated in or modulatory of TGF response. Therefore, it is not clear whether the $[Ca^{2+}]_i$ increase in the mesangial cells has relevance for the TGF mechanism.

In addition to autoregulation, the shear stress response of the vasculature also shows a purinergic signaling component (63, 64). Shear stress to endothelial cells releases nucleotides and via P2 receptor activation elevates $[Ca^{2+}]_i$ in the endothelial cells resulting in vasodilatation. This response has been suggested to be mediated both via the $P2X_4$ (65) and the $P2Y_2$ receptor (707). Recently, the $P2X_7$ receptor has been implicated as a mediator of vasoconstriction of resistance arterioles (414). Studies from Menzies et al. showed that an antagonist with some selectivity towards the $P2X_7$ receptor (BBG) acutely reduce the systemic blood pressure and the pressure natriuresis threshold in Fisher rats (F344) both at baseline (415) and after exposure to AngII infusion for two weeks (414). This finding could be reproduced by the seemingly more selective $P2X_7$ receptor antagonist, AZ11657212 (414). This antagonist not only acutely lowered blood pressure but also increased the renal blood flow and oxygen delivery to the renal medulla. The latter was ascribed to a direct effect on vasa recta, which are known to contract in response to ATP in a partially $P2X_7$ receptor-dependent fashion (100).

Thus, purinergic signals, in general, have a substantial impact on the regulation of the renal blood flow and in the maintenance of the renal function. This signaling system is receiving input from a large number of the other paracrine signaling systems afoot in the kidney. In terms of the autoregulation, it is particularly prostaglandin and NO signaling. The general rule is that substances that lead to renal vasodilation cause desensitization of the renal autoregulation, whereas vasoconstrictors sensitize the autoregulation (Fig. 2).

2.3 Local vasoactive peptides

Vasoactive peptides are some of the most potent regulators of vascular diameter. Overall, these peptides, particularly AngII as an effector of the RAAS and its opponent, the kallikrein-kinin system, are essential in the overall blood pressure regulation. Circulating AngII is also a keen modulator of renal autoregulation. Similar to other vasoconstrictors of afferent arteriole AngII sensitizes the TGF-mechanism, and thus, indirectly modifies the impact of renal paracrine signaling. Both RAAS and the kallikrein-kinin system have, in addition to the systemic effects, been suggested to be paracrine effector systems for regulation of renal tubular function and will be discussed below, including potential interaction between the tubular and the vascular system. The circulating peptides are for this review considered part of the systemic vascular regulatory system and not discussed further. One exception is endothelin, because of its pronounced expression and functional role in renal tubules, it is likely that tubular endothelin release has marked local effects in the renal vasculature.

Endothelin

Endothelin is the newest addition to the vasoactive peptides with distinct effects on renal function. It was first sequenced in 1988 (746) and identified as the previously described endothelial-dependent vasoconstriction factor (116, 253). Now, endothelin is known to be produced by and act as a paracrine signaling molecule in a large variety of cell types,

like renal epithelial cells (331), β-cells in islet of Langerhans (476), bone marrow-derived cells (142, 589), cardiomyocytes (177, 286), lung (390) and brain (202), making its name slightly misleading. The family of endothelins consists of three members ET-1, ET-2, and ET-3, of which ET-1 is the most thoroughly investigated. They are all 23 amino acids long, synthesized as and cleaved from prepropeptides. This is described in detail for ET-1, where preproET-1 (289), which is further processed by endothelin converting enzyme present in the cytosol of both endothelial- and smooth muscle cells (298, 553). In the context of the renal vasculature, it is important to emphasize that ET-1 has been explicitly shown to be produced by endothelial cells in the glomerulus as well as other parts of the renal microvasculature (307). ET-1 is known to be released primarily to the basal side of the endothelial cells in direct vicinity to the smooth muscle cells (701), even though the release mechanism has, at present, not been firmly established. The endothelins elicit their action via ET_A and ET_B receptors, although with different affinity. The ET_A receptor is primarily activated by ET-1, but also with reduced affinity by ET-2, whereas all three peptides activate the ET_B receptor with equal affinity (15, 558). In the vasculature, ET_A is exclusively expressed in the smooth muscle cells (264), where ET-1 via a direct effect is one of the most potent vasoconstrictors. This general pattern apparently also applies to the renal vasculature, at least in rats and humans (111, 726). ET_A receptors are coupled to G_q-proteins and, thus, cause constriction of smooth muscle cells via an increase in inositol triphosphate IP_3 (535, 693) and subsequent intracellular Ca^{2+} concentration and protein kinase C (PKC) activation (216). Substantial data has supported that ET-1 mediated Ca^{2+} signaling mainly occurs via cyclic adenine diphosphate ribose (cADPR) cyclase/ryanodine receptor–activating pathway (16, 159). Surprisingly, the signal transduction pathway is not equally well elucidated for ET_B. It is known to increase NO production in endothelial cells via stimulation of nitric oxide synthase (eNOS), which would be expected to be preceded by an increase in $[Ca^{2+}]_i$. However, the increase in $[Ca^{2+}]_i$ is relatively modest after selective stimulation of the ET_B receptor compared to selective ET_A receptor stimulation (510). An interesting aspect of ET-1 signaling is that the ET_B receptor has been suggested to muffle the ET-1 mediated ET_A stimulation. It has been shown that deletion or pharmacological inhibition of ET_B increases the circulating ET-1 levels, and thus, ET_B modifies the ET_A-induced vasoconstriction both by endothelial-dependent vasodilation and by direct sequestering of ET-1 through binding to ET_B receptors (312).

It is challenging to give a precisely weighed analysis of the importance of an individual set of receptors in all isolated portions of the renal vasculature and how the respective elements contribute to the overall effect of endothelin on the renal blood flow. The glomerular filtration rate is kept constant by the myogenic response in the afferent arteriole and the TGF mechanism that constitutes renal autoregulation. However, vasoactive components like AngII, various prostaglandins, NO and adenosine, are known to modulate the sensitivity of the autoregulatory processes (for review see (437), Fig. 2). Notably, the kidney is particularly sensitive to ET-1 (94), where ET-1 causes a reduction of both the overall blood flow and GFR as a consequence of vasoconstriction (63, 101, 155, 511). It has not been wholly settled whether the afferent or efferent arteriole is more sensitive to ET-1 but deduced from the functional data the efferent arteriole must be more sensitive because a low dose of ET-1 reduces renal blood flow without affecting the GFR (315). This notion is parallel to what has been shown for AngII (110). The effect of ET-1 on the overall renal blood flow and GFR is likely to result from activation of the ET_A since infusion of a selective ET_A antagonist abolishes the ET-1 effect, whereas ET_B has little if any effect in dogs and rabbits (63, 155). Although ET-1 also causes vasoconstriction of the afferent arterioles in rats, there is a substantial contribution from the ET_B receptor (101, 199, 284, 301, 725). Interestingly, it has also been shown in rats that under cover of a specific ET_A receptor antagonist, injection of ET-1 actually elicit an elevation of GFR and renal blood flow, supporting that this procedure may tease out an ET_B receptor-dependent endothelial-mediated vasodilation (301). This notion is supported by data that demonstrate that selective ET_B receptor agonist directly causes vasodilation of the efferent arterioles from rats (284). To sum up, these findings show that ET-1 primarily causes an ET_A receptor-dependent vasoconstriction of the afferent arteriole, which is partially modified by an ET_B/endothelia-dependent vasodilation of the efferent arteriole.

In addition to the effects of ET-1 on the afferent and efferent arteriole, ET-1 also affects the renal perfusion by modifying the microcirculation. As mentioned, newer data support

that the contractile state of the capillary pericytes modify the overall resistance and thereby effectively the perfusion of the tissue. This has been mainly promoted for the brain (228) but has, in a few strong papers, also been proposed for the medullary perfusion in the kidney (423). Both the ET_A and the ET_B receptors are expressed in the vasa recta with a pattern that mirrors what has been described for the arterioles. Thus, the ET_A receptor is mainly expressed by pericytes, whereas the ET_B receptor is primarily expressed by the endothelial cells (342, 726). A single study shows that this expression is also functionally relevant. In freshly dissected vasa recta, ET-1 causes vasoconstriction already at a concentration of 10^{-16} M, with a potency that surpasses both ET-2 and ET-3, even though they were also found to have distinct vasoconstrictor effects (602). These data have been confirmed in the kidney slice model, where ET-1 caused constriction at the sites where pericytes were identified (99). These data indicate that ET-1 can have a regulatory effect on the perfusion of the medulla. Because the overall effect is constriction of the capillary bed, ET-1 would be expected to be released in a situation where there is a need for urinary concentration and reduced wash out of the papillary osmotic gradient. In this context, it is interesting that ET-1 has been shown to be produced in high amounts in the inner medulla collecting duct (686), as discussed later. This opens for the possibility that local events in the collecting duct may influence the degree of contraction of the vasa recta as suggested in a review from Speed et al. (624).

The data mentioned above provide compelling support for applied ET-1 being able to modify renal perfusion. If ET-1 is to act as a paracrine factor, it should be possible to detect an effect of endogenous ET-1 on the renal perfusion parameters. Several studies in rats, however, find that ET_A receptor antagonists do not alter either the renal blood flow or the GFR in conscient animals (405, 511, 522). Opposed to this, selective inhibition of ET_B receptors alone has been shown to reduce the renal blood flow in anesthetized rats (405). This suggests that *in vivo* endogenous ET-1 primarily acts on endothelial ET_B receptors with a following reflexive effect on the smooth muscle cells. Unfortunately, these data have not been verified in genetically modified animals, which would be very helpful in settling the overall effect of ET-1 on the regulation of renal perfusion and in the conceptual verification that endothelins actually are relevant paracrine signaling molecules for the vascular kidney. Interestingly, the expression of ET receptors in rodents is altered by variation of salt intake. Both protein expression and function of the ET_B receptor in the afferent arteriole are elevated in rats on a high NaCl diet (284, 575), resulting in a more pronounced ET_B-mediated vasodilation of the afferent arteriole. This again underscores that *in vivo,* the ET-1 working at ET_B receptors favors endothelial-dependent vasodilation. This could potentially result in increased renal perfusion during a high NaCl diet, which in principle would support increased NaCl excretion by the kidney. Regarding the *in vivo* effects of endothelins, it is surprising that the overall effects of selective ET_A stimulation comprise hypotrophy of the kidney, local renal inflammation, and proteinuria with following renal fibrosis (85, 149, 560, 561). To add to this complexity, endothelin signaling interacts with almost all of the paracrine signaling systems. This is particularly true for NO and purinergic signaling systems, which extensively modify the integrated response to the endothelins. These interactions will be discussed further below.

2.4 Renal vasculature and reactive oxygen species

In addition to NO, other gaseous signaling molecules have been demonstrated to impact renal function markedly. Reactive oxygen species are byproducts of normal cellular metabolism, such as mitochondrial oxidative phosphorylation or formed by NAD(P)H-oxidases, P450 monooxygenases, lipoxygenases, cyclooxygenases, xanthin oxygenases and by nitric oxide synthases (for review see (556). The cells are protected against these reactive components via superoxide dismutase (in the case of O_2^-), whereas catalase, glutathione peroxidase, and peroxiredoxins/thioredoxin reductase degrates H_2O_2 (for overview, see (133, 179)). Reactive oxygen species involved in renal cell injury are primarily released from macrophages and neutrophils (576, 650). Already in the 80'ties, it was shown that reactive oxygen species play a role in acute glomerular cell damage (58, 297, 527, 750). Not surprisingly, reactive oxygen species have also been shown to be essential in proximal tubular damage inflicted by, for example, myoglobin (754).

The demonstration that reactive oxygen species are responsible for a major part of renal injury inflicted by infusion of AngII (239, 703) sparked a marked interest in the biology of this effector system because it suggests that reactive

oxygen species may not only be relevant in pathophysiological conditions. Newer data suggest that mainly the tubular function is modified by local endogenous superoxide and H_2O_2 production. The spatial proximity of the renal tubular and vascular system excludes a paracrine signaling molecule to work selectively in one of the systems unless there is a differential receptive profile. Therefore, one would expect these substances also to affect the vasculature. It has been demonstrated that the unstimulated interstitial concentration of H_2O_2 is around 55 nM in the cortex and approximately the double in the medulla (89), which supports that the renal interstitium has a baseline level of reactive oxygen species under physiological conditions *in vivo*. Overall, production of O_2^- causes vascular smooth muscle cell contraction and reduces the endothelial-dependent vascular relaxation (178, 323, 368, 419, 703), whereas H_2O_2 cause relative vasodilation via effects on the endothelium. These effects include upregulation NOS in the endothelial cells (176) and enhanced release of endothelium-derived hyperpolarizing factor (176, 379). It was demonstrated that inhibition of superoxide dismutase (SOD) causes hypertension and a reduction of renal plasma flow (723), which could be prevented by scavenging of O_2^- in the inner medulla (394). The logical conclusion of these data is that under physiological conditions, O_2^- is present at relevant concentrations in the renal tissue to ensure relative vasoconstriction in the inner medulla.

In the vasculature, one can always discuss whether relevant signaling molecules are truly locally produced in the organ or whether they are a part of the overall systemic cardiovascular regulation. A strong argument for paracrine signaling in the renal vasculature is whether a given component is important for TGF because this mechanism involves interaction between the tubular and vascular systems. Interestingly, reactive oxygen species have also been proposed to have an impact on the TGF response, where increased O_2^- production in macula densa has been shown to sensitize TGF (723, 724), which, as mentioned, is typical for substances that cause vasoconstriction in the afferent arteriole. A metaanalysis of the effect of the O_2^- scavenger tempol shows that this substance in a relevant concentration cause a 27% reduction in the TGF (290). The standard deviation on this result was relatively high, which minimizes the overall effect of tempol on TGF. In terms of the myogenic response, O_2^- and H_2O_2 have been shown to differentially modify afferent arteriolar reaction to a sudden increase in the perfusion pressure (370, 371). O_2^- generation potentiates the myogenic response by activating Ca^{2+} activated Cl^-channels in a PKC-dependent manner, whereas H_2O_2 reduces the myogenic response through PKG-dependent activation of voltage-gated K^+ channels (371). Interestingly, stretching of vascular smooth muscle cells has been shown to release O_2^- (88, 279, 422), and thus potentially could mediate the myogenic response. Based on these observations, one can conclude that O_2^-, like $P2X_1$ signaling, primarily affects renal autoregulation through modulation of the myogenic response. Thus, taken together, the reactive oxygen species have to be considered for the integrated physiological understanding of renal paracrine signaling.

2.5 Vascular eicosanoids–impact on renal function

Prostaglandins are ubiquitous signaling molecules that can act both as hormones with targets farther away from the production point and/or work in local autocrine/paracrine signaling. Prostaglandins are *de novo* synthesized from arachidonic acid generated in the membrane of practically all cell types (Fig. 3). Prostaglandin H_2 is the first-generation prostaglandin generated as a function of either cyclooxygenase (COX) type 1 or type 2 and further converted into prostacyclin (PGI_2), thromboxane A_2 (TxA_2), prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) by their respective synthases (183, 734). Prostaglandins are notoriously associated with inflammation, and bone marrow-derived cells have a larger capacity for prostaglandin generation than other cell types partly because of a higher baseline activity of non-inducible COX1. Classically, prostaglandins are essential in the development of the rubor, calor, tumor, dolor response to infection/inflammation (for review see (537)). The associated redness and edema of the skin report about underlying sustained vasodilation. Therefore, it is not surprising that prostaglandins have a marked effect on the diameter of the resistance vessels and the regulation of endothelial permeability. Generally, these arachidonic acid derivatives work through either G_s or G_q-coupled receptors, which have opposing effects in smooth muscle cells. The G_q-coupled receptors will cause an IP_3-dependent increase in $[Ca^{2+}]_i$ and via calmodulin increase the myosin light chain kinase activity and subsequent power stroke in

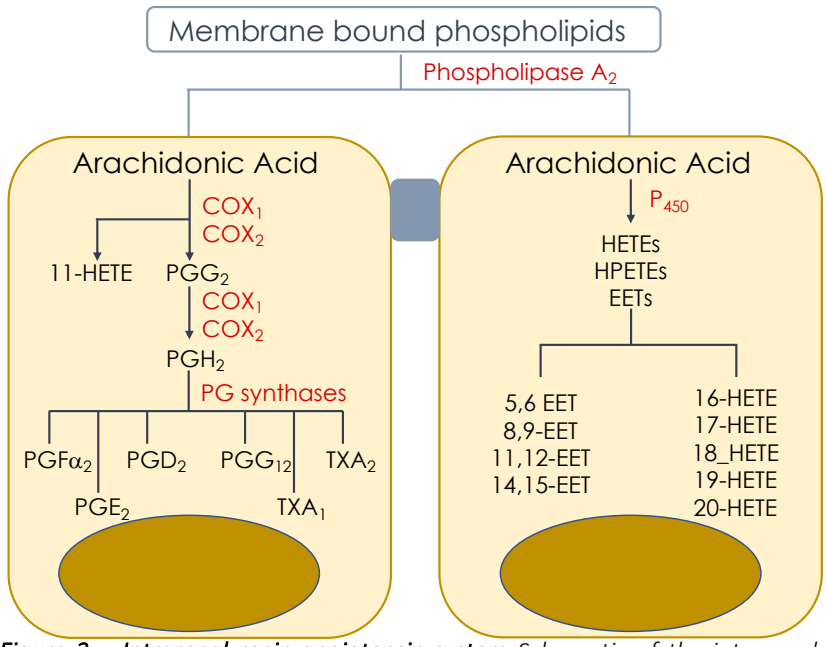

Figure 3 – Intrarenal renin-angiotensin-system *Schematic of the intrarenal renin-angiotensin-system showing the filtration of the essential components of the system. They are taken up into the PT cells that allow conversion of the angiotensinogen produced in the liver to AngI and further to AngII by the angiotensin-converting enzyme expressed in PT. AngII can be taken up from the basolateral side via the A_1 receptor. The AngII released from the proximal tubule is either taken up by the cell from the tubule fluid, or the interstitium or it is converted by internalized precursor and enzymes. Thus, the intrarenal RAS is not a bona fide paracrine signaling system in the kidney.*
Abbreviations: ACE (Angiotensin-converting enzyme), AngI (angiotensin I), AngII (angiotensin II), A_1 (angiotensin receptor 1), PRR (prorenin/renin receptor).

the smooth muscle cells. In contrast, the G_s activation will increase the adenylyl cyclase activity, generation of cAMP, and PKA activation. This will, in turn, reduce the Ca^{2+}-calmodulin induced MLCK activation by decreasing the affinity of the Ca^{2+}-calmodulin complex to MLCK (525). Therefore, the net result of prostaglandins on the vasculature of a given tissue will depend highly on the profile of prostaglandins present locally and the expression pattern of prostaglandin receptors. The family of prostaglandin receptors includes the PGE receptors (E prostanoid receptor 1 (EP_1), EP_2, EP_3, and EP_4), PGD receptor (DP1), PGF receptor (FP) and PGI receptor (IP) (435). In the kidney, the most intensively studied prostaglandins are PGE_2 and PGI_2 (prostacyclin). These are both produced by the renal vasculature and are generally believed to cause renal vasodilation (34, 70, 139, 251, 463, 655), although one study does report PGE_2 to cause vasoconstriction in the afferent arteriole (282). Prostaglandins are prone to reach the kidney through the circulation, and therefore here we only regard the renal autoregulatory component as a true paracrine effect even though this may easily be an oversimplification.

Regarding the TGF response, COX_2 has been demonstrated to be almost exclusively expressed in the macula densa (236). Inhibition of COX activity markedly reduces both the TGF response (577) and renin-secretion from the JG cells (213). An early study shows that PGE_2 apparently is released in response to an altered Na^+ and Cl^- concentration in the tubular lumen at the site of the macula densa (498). This potentially suggests that COX_2 is active at the macula densa site and can produce prostaglandins in relevant amounts. However, it turns out that the COX_2 cleaving product that has the most sizable effect on renal autoregulation via TGF is thromboxane A_2 (577).

As mentioned above, there are additional tubular segments that influence renal blood flow in a paracrine fashion. Regarding the eicosanoid signaling, it is important to underscore the crosstalk between the connecting tubule (CNT) and the afferent arteriole, which has been shown to get into close contact with the afferent arteriole (30). This system is referred to as the connecting tubule-glomerular feedback (CNTGF) system, even though it does not provide feedback but rather is a feedforward system essentially counteracting or modifying the TGF mechanism. The CNTGF was originally demonstrated in dissected and perfused glomeruli with an attached connecting tubule, which was also cannulated and perfused (532). Ren et al. showed that increasing the $[Na^+]$ of the perfusate of the connecting tubule from 5-40 mM caused vasodilation of afferent arterioles pre-constricted with norepinephrine and that this response was inhibitable with amiloride/benzamil (532, 705). *In vivo*, CNTGF has been used to explain a slow-developing increase in renal blood flow in response to an acute increase in perfusion pressure in rats with clamped plasma levels of AngII (586). This implicates that an increased ENaC-mediated Na^+ reabsorption results in increased renal blood flow, and thus, would primarily function as a systemic valve to rid the body of Na^+ in a situation where there is sizable Na^+ reabsorption. Dilation of the afferent arteriole will increase the filtration and

thereby the production of pre-urine. Increased pre-urine production will subsequently deliver more Na^+ to the distal segments of the kidney, and thus the system constitutes a feedforward system accelerating the renal Na^+ excretion. Interestingly, this feedforward mechanism has been demonstrated to be mediated by PGE_2 release from the CNT (530) inflicting vasodilation via EP_4 receptors on the smooth muscle cells of the afferent arteriole (531). The question is how this paracrine mechanism reads into the overall regulation of renal function and body homeostasis. In this context, it is relevant in what situation this mechanism is activated.

Interestingly, the luminal [Na^+], at which a corresponding dilation, is observed is low for the connecting tubule (CNT). In the distal convoluted that feeds into CNT, the [Na^+] concentration has in 18 micro-puncture studies been estimated to be in the range of 35-72 mM (210). Although these values may overestimate the [Na^+] in the CNT, they suggest that CNTGF is likely to be active under baseline conditions. This notion is supported by experiments using the stopped-flow technique (705). Thus, the degree of renoprotection provided by the TGF mechanism happens on a background of a dilatory tone provided by the transport function of CNT in the described a feedforward manner. Based on this, CNT-GF has been proposed to be responsible for the resetting of the TGF response that occurs in conditions like hypertension and high salt intake (704).

A more recent aspect of COX_2 function in macula densa points to an essential role for COX_2 in the regulation of the number of renin expressing cells in the kidney. Apparently, CD44 positive cells with mesenchymal stem cell properties migrate into the afferent arteriole area and gain renin releasing properties when mice were kept on a low salt diet combined with an ACE inhibitor (706). Moreover, renin producing progenitor cells may also repopulate the glomerular area in response to podocyte injury and give rise to generation of new glomerular epithelial cells (502). Interestingly, the recruitment of CD44 positive cells under a low NaCl diet requires macula densa dependent COX_2 activation and PGE_2 release (748). These findings are remarkably interesting in terms of the overall modulation of renal function. Although it does not report a direct effect of acute paracrine signaling immediately modulating renal water and salt handling, the long-term modulations may allow at least mice to live under low salt conditions while keeping homeostasis. Collectively, prostaglandins primarily are mediating vasodilatory effects in the kidney that modulate the classical renoprotective autoregulation.

Thromboxane A_2 is a potent vasoconstrictor, and interestingly inhibition of TxA_2 synthase markedly reduces the vasoconstrictor properties of Ca^{2+} ionophores and acetylcholine (201, 205, 309). This nicely illustrates the paracrine signaling effect of TxA_2 in response to an increase in $[Ca^{2+}]_i$. Thus, an $[Ca^{2+}]_i$ increase stimulates the phospholipase A_2-dependent conversion of arachidonic acid to prostaglandin precursors primarily in the endothelial cells, allowing TxA_2 to contract the underlying smooth muscle cells. TxA_2 is, as mentioned, one of the most potent vasoconstrictors, acting on selective TP receptors on the vascular smooth muscle cells. Even though the TP receptor is most sensitive to TxA_2, it can also be activated by PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2 in high concentrations (158). This mode of action suggests that TxA_2 primarily is a paracrine signaling molecule. One has to bear in mind that TxA_2 is closely associated with thrombocyte activation, and thus, a primarily intravascular agonist, which means that TxA_2's effect on the renal circulation could result from bulk TxA_2 in the bloodstream. The endothelium, as the primary source of TxA_2, is supported by its effects on the TGF response. Inhibition of either TP receptors or the TxA_2 synthase, on average, causes some 28% reduction of the TGF response (577). It is, however, striking that interference with TxA_2 signaling is more effective from the lumen of the vasculature rather than the tubule (577).

Other arachidonic acid derivatives
Hydroxyeicosatetraenoic acid (20-HETE) is specifically generated from arachidonic acid in the liver and the kidney as a consequence of the catalytic activity of the P450 system (CYP4A and F, for review, see (548)). Twenty-HETE acts via the G_q coupled receptor GPR75 (276), which is expressed both in smooth muscle cells and on the endothelium (188). In the renal vasculature, 20-HETE is known to constrict juxtamedullary afferent arterioles (277). One would immediately think that the $[Ca^{2+}]_i$ increase inflicted by the G_q activation would be sufficient to cause the vasoconstriction, but apparently 20-HETE instead inhibits $K_{Ca}1.1$ channels in a PKC dependent manner (641), which trigger a depolarization-induced opening of voltage-dependent Ca^{2+} channels (774) and TRPC6 (280)

subsequently increasing $[Ca^{2+}]_i$. Interestingly, GPR75 was identified as the 20-HETE receptor long after the functional effects of 20-HETE on smooth muscle cells were described. In this context, it worth noting that original data on 20-HETE-induced $K_{Ca}1.1$ channel inhibition was shown in cell attached-patches of renal smooth muscle cells and thus, showing channel inhibition despite the simultaneous increase in $[Ca^{2+}]_i$. Surprisingly, 20-HETE in endothelial cells supports the direct vasoconstrictor effect of 20-HETE. Apparently, the Ca^{2+}-induced activation of mitogen-activated protein kinase (MAPK) inhibiting eNOS dominates over the Ca^{2+}-induced activation of the enzyme and thus, causing some degree of endothelial dysfunction (90).

20-HETE has because of its distinct formation in the kidney been implicated in renal autoregulation. In rat cerebral circulation, 20-HETE has been suggested to mediate the myogenic response to sudden arteriolar distension (196). The study demonstrates that stretching of the vascular structure results in a substantial release for 20-HETE (196), and inhibition of the synthesis essentially abolishes the myogenic response in cerebral arteries (196). This finding can be extrapolated to the kidney, where inhibition of 20-HETE signaling substantially reduced the pressure-induced vasoconstriction in afferent arterioles (194, 529). In this study, the authors suggested that 20-HETE acts downstream of ATP signaling and that 20-HETE has a permissive effect for the myogenic response in the afferent arteriole (529). However, 20-HETE has been demonstrated to specifically reduce the $P2X_1$ receptor-dependent Ca^{2+} signaling and vasoconstriction of afferent arteriole (766, 767), and thus, at this point, it is reasonable to suggest a synergistic effect of the two mediators.

Regarding the TGF, 20-HETE has been reported to elicit quite substantial effects. Preventing the action of 20-HETE, by ω-hydrolase inhibitors or by 6,15-20-hydroxyeicosadienoic acid that is used as an antagonist for the actions of 20-HETE, causes a staggering 80% reduction in TGF as substantiated in a metanalysis of the available data (194, 577, 775). This means that similar to 20-HETE and $P2X_1$ receptor activation in the myogenic response, interference with 20-HETE or adenosine signaling both almost abolish the TGF response. However, it is still not known to what extent these events are coupled or interacts. Endogenous 20-HETE generation is exceedingly recognized as essential for renal autoregulation and, thus, the renal perfusion.

In summary, the common denominator for all the discussed vascular paracrine signaling molecules is that they are either mediate or modify renal autoregulation (Fig. 2). Since renal autoregulation protects the kidney against pressure-induced damage, the paracrine factors that either mediate autoregulation or sensitize the response can be viewed as reno-protective. In contrast, the mediators that desensitize the autoregulation potentially renders the kidneys more vulnerable to high-pressure damage. When looking for an overall trend for all the autocrine/paracrine vasoactive components discussed, there is an overweight of vasoconstrictors (see table 1). This collectively fits the notion that paracrine factors released in response to external stimuli tend to protect the kidney by reducing the amount of filtered load and reduce the stress on the filtration barrier. It has to be emphasized that all the vasoconstrictors work on the background of the renal autoregulation, and thus, it would be fair to use the term 'sensitizers of autoregulation' instead of vasoconstrictors illustrating that they reduce but do not have the ability to prohibit renal blood flow.

Nevertheless, sensitization of the TGF response will also reduce renal oxygen supply to the epithelial cells. This is, to some extent, be balanced by the reduced filtration, which limits the

Effect of paracrine factors on diameter of afferent arteriole

Paracrine factors	Constriction	Dilation	Reference
Adenosine	+++	+	7, 68,238, 528, 601, 666
ATP	++		283, 690
Endothelin	+++		63, 101, 155, 216, 511, 535, 693
H_2O_2		+	176, 379
HETEs	++		277, 641, 744
Nitrc oxide		+ +	47, 73, 310, 675
O_2^-	++		178, 323, 368, 419, 703
Prostaglandines	+	+	Cons: 34, 70, 139, 251, 463, 655 Dilat: 282
Thromboxane A_2	+++		201,205, 309

Table 1

amount of pre-urine in the tubular system and thus, also the O_2 consumption needed for transport. This will essentially allow the epithelial cells to prioritize the delivered O_2 for self-maintenance rather than for transport function. The question is whether the reduction in tubular flow is sufficient to secure protection of the epithelial cells against the reduced O_2 delivery? Our key proposal in this review is that true and comprehensive reno-protection requires a defense mechanism for the epithelial cells, where they can reduce transport when stressed.

3. Paracrine signaling in the renal epithelia

Continuing the reflection on epithelial self-preservation, one could consider the notion that paracrine factors in the kidney serve as a toolbox for self-protection. If this was the case, the paracrine factors should be able to effectively reduce the renal transport processes preserving energy for self-maintenance and thereby reduce the risk of tubular cell death. Thus, for optimal reno-protection of both the filtration barrier and the tubular system, the paracrine factors that show a profile of vasoconstriction/TGF sensitization and epithelial transport inhibition will serve this overarching purpose. Therefore, the following section deals with the various paracrine factors and their effect on transepithelial transport.

3.1 Tubular purinergic signaling

As mentioned in section 2.2, all elements of the purinergic signaling system are expressed and functional in the kidney. The power of this signaling system is illustrated by its central position in the renal autoregulation via the TGF mechanism. The signal events in the TGF mechanism clearly illustrate that epithelial cells are able to release ATP in a regulated and non-lytic fashion (336). Thus, the purinergic signaling system meets all the requirements to be an effective paracrine signaling system in the kidney. It comprises 1) regulated release of the relevant signaling substance, 2) specific receptors (P0, P1, and P2) for ATP and its derivatives and effective enzymatic degradation of ATP for termination of the signals.

Adenine signaling in renal epithelia

Recently, adenine has been proposed to be a ligand for a new family of receptors, the P0 receptors, and thus, may compromise an evolving element of the purinergic signaling system in the kidney. The adenine receptor was first described by Bender et al. in 2002 (42) and later cloned and characterized pharmacologically (661, 698). At least in rats, H^3adenine binding sites were found the kidney at moderate levels as compared to the central nervous system, where it was initially identified (716). Renal expression has been confirmed on mRNA level in the deep inner cortex, inner and outer stripe of outer medulla, and by immunohistochemistry with an antibody, which on western blot shows one or two bands in the named areas, which was partially removed by peptide pre-adsorption (321). In terms of tubular labeling, this antibody primarily stained the apical membrane of principal cells of the collecting duct (CD) (321). One unresolved question is, where the potential substrate may come from?

Interestingly in humans, adenosine is degraded to inosine and further to hypoxanthine and not to adenine (630). However, several bacteria, including uropathologic *E. coli*, are able to degrade AMP and adenosine to adenine via AMP nucleosidases (364). Thus, adenine appears not directly to be a part of the purinergic signaling systems, because it does not share the same release and extracellular degradation mechanisms that are elementary for trigger P1 and P2 receptor activation. In mammals, adenine is produced in the cytosol during polyamine synthesis and would have to be released to the extracellular space to exert its actions. This could, in principle, occur via specific transporters or through larger pores such as connexin hemichannels or pannexins, but evidence for adenine release is pending. It must, however, be noted that the intracellular concentration of adenine in mammalian cells is likely to be very low because it is rapidly incorporated into various adenine containing compounds. Thus, short opening of connexins/pannexins is unlikely to change the extracellular concentration of adenine markedly as compared to ATP with its cytosolic concentration of 1-4 mM. That said, the kidney excretes around 11 µmol adenine (10.4 µmol (62) – 11.4 µmol (230)) over 24 hours and thus, there is a concentration of 5-10 µM in the final urine. This should potentially be

sufficient to ensure some baseline adenine receptor activation in CD. Moreover, the intracellular concentration of adenine in *E. coli* is 1.5 μM (43) and may be a potential source of adenine during urinary tract infections.

There is presently very little clue as to what the adenine receptor might do in the kidney. However, it has been shown that the normal plasma concentration of adenine is around 70 nM and increases to over 1 μM during renal insufficiency (616). Interestingly, the primary paper on adenine receptors in the kidney demonstrated that adenine (10 nM) reduced the desmopressin (dDAVP) induced cAMP generation in suspensions of rat inner medulla collecting ducts (IMCD). The P0 receptor antagonist PSB-08162 prohibited this effect (321). This potentially implies that adenine may be a luminal signaling molecule either secreted by the renal epithelial cells or filtered, which could modify the urinary concentration ability of the kidney. However, adenine may turn out not to be a true paracrine factor despite its suggested effect on renal transport, if it is only relevant for bacterial/host interaction.

Adenosine receptors in epithelial function

Adenosine receptors are widely expressed in the renal tubule and influences the tubular function. In the proximal tubule (PT), adenosine activates solute and water reabsorption via the A_1 receptor. This effect was nicely documented in isolated, perfused PT by a clear inhibition of tubular transport in the presence of a selective A_1 receptor antagonist (722). A survey of the literature by Maughan and Griffin (407) has shown that a higher dosage (>250 mg) of the non-specific adenosine antagonist caffeine is needed to trigger diuresis in humans and that normal caffeine intake is generally not considered to affect the fluid balance. One explanation is that frequent caffeine consumption results in a desensitization of the potential diuretic effects of caffeine (407). Nevertheless, caffeine in higher dosage does cause diuresis in humans (441) and in mice (539) when not recently been pre-exposed to caffeine. More selective inhibition of A_1 receptors consistently causes diuresis in rats (329, 729) and humans (29), which is congruent with the finding that the diuretic and natriuretic effects of caffeine requires the A_1 receptor as shown in A_1 receptor-deficient mice (539). Interestingly, and opposite to the effect of P2 receptors, adenosine receptors stimulate the renal tubular transport function. The adenosine-mediated activation in the PT was suggested to result from stimulation of apical NHE_3 (124). Recently, the caffeine-induced diuresis was found to be similar in the tubular specific NHE_3 (PT and TAL) knock out mice (160), which calls for an alternative explanation that may include activation of the basolateral electrogenic Na^+-$3HCO_3^-$ cotransport (NBCe1-A/ SLC4A4) (651). The stimulation of PT transport by adenosine receptor activation has been substantiated *in vivo*. Direct injection of A_1-receptor antagonists or adenosine deaminase in PT *in vivo* reduced the PT fluid reabsorption (345). Surprisingly, the A_1 receptor knockout mouse had similar PT liquid handling as the wild type littermate controls (124), which suggests a compensation in A_1 deficient mice. Taken together, all data indicate that extracellular adenosine stimulates the transport function of PT.

Opposite effects of adenosine are observed in TAL. Activation of A_1 receptor by adenosine (10 nM) reduces the transepithelial Cl^- transport by 50% independent of prior arginine vasopressin (AVP) stimulation in rat TAL (35). This study also demonstrates that the HCO_3^- reabsorption is unaffected by adenosine (35) and thus, is consistent with the lack of involvement of NHE_3 in caffeine-induced diuresis mentioned above (160). In TAL, this transport inhibition is intuitive because it has been shown that adenosine is released from the epithelial cells during hypoxia (36). The mTAL is situated in a less well-perfused area of the kidney, and thus, it is important for this segment to adjust its transport and energy consumption to the factual oxygen supply. In this context, it is interesting that selective A_1 receptor stimulation reduces cAMP production in freshly isolated and cultured cells from rabbit and mouse mTAL (33, 71), whereas more selective A_2 receptor agonists increase cAMP production at higher concentrations (71). Despite the difference in cAMP generation, both A_1 and A_2 receptor stimulation increased $[Ca^{2+}]_i$ and IP_3 generation (71). A later study places these slightly contrasting results into perspective. Apparently, adenosine released in response to hypertonic Na^+ and Cl^- concentration potentiate AVP-induced cAMP production in mouse mTAL in an A_2 receptor-dependent fashion (33) and thus, would be expected to stimulate transport in TAL further. It must be emphasized that this study supports that adenosine at lower concentrations reduces cAMP production in an A_1 dependent manner (33). The presence of two adenosine receptor subtypes in TAL has been confirmed with RT-PCR on microdissected renal tubules from rats and mice, i.e., the A_1 (697,

744) and A_{2B} (697). Collectively, these data indicate that lower concentrations of adenosine inhibit and higher concentration stimulate TAL transport. As indirect support for this notion, it was found that higher concentrations of adenosine receptor agonists stimulate the activity of renal outer medullary potassium channel (ROMK) (367) as well as stimulate a basolateral 50 pS K^+ channel (221), which is consistent with transport stimulation. These effects could not be prevented by A_1 receptor inhibition but appear to be mediated by the A_{2A} receptor. The only inconsistency in these findings is that the A_{2A} receptor has not been identified in TAL (697).

Little is known about the effects of adenosine in the thin limbs of the loop of Henle and DCT except for the presence of a strong signal for A_1 receptor mRNA in the both the descending and ascending thin limb isolated from rat and mice (361, 697). In DCT, mRNA for A_1 is found in the rat as well as A_{2B} in both rat and mouse (697). In DCT cells isolated from immorto-mice it was shown that adenosine (10 μM) stimulated Mg^{2+} transport via the A_2 receptor (304). The same study revealed that A_1 receptor stimulation reduced the PTH-induced Mg^{2+} transport (304) following the same pattern demonstrated for TAL.

Adenosine plays a role in fine-tuning of Ca^{2+} reabsorption in DCT and connecting tubule. It has been shown that adenosine increases the Ca^{2+} reabsorption in primary cultured rabbit connecting tubule cells (CNT) and in the CD via activation of A_1 receptors (261) and subsequent activation of a phorbol-ester insensitive PKC (260). In terms of the CD, the natriuresis produced by A_1 receptor inhibition in PT does not trigger increased urinary K^+ secretion in rats (200, 458) as one would expect from an increased volume and Na^+ load to the CD. This observation has alluded to the fact that the CD has been shown to expresses A_1 receptors (361, 490, 697, 744), suggesting that adenosine via A_1 receptor may inhibit the epithelial Na^+ channel (ENaC) in the CNT/CD. Accordingly, adenosine has been shown to inhibit ENaC function through A_1 receptor activation in primary culture of rat IMCD (741) and split open rat cortical collecting duct (CCD)(718). In this study, the ENaC inhibition was suggested to be brought about via phospholipase A_2 activation and consecutive degradation of arachidonic acid and generation of 11,12-epoxyeicosatrienoic acid (EET)(718). Studies of primary cultures of rat IMCD revealed that adenosine via A_1 receptors concentration-dependently reduces AVP-induced cAMP production (743). This study was substantiated by data from a human CCD cell line suggesting that adenosine in itself triggers an increase in intracellular cAMP and that this stimulation is mediated via A_2 receptors, whereas A_1 receptor activation counteracted the glucagon-induced increase in cAMP (518). This is in line with a biphasic adenosine effect reported for the other renal segments. Because adenosine also in this segment can decrease the intracellular level of cAMP and dampen AVP-induced signaling, one would expect that water permeability to be influenced by the extracellular adenosine level. Consistent with this notion, adenosine in nanomolar concentrations reduced AVP-induced water permeability in perfused rat IMCD (141). This effect was confirmed to be exclusive to basolateral application of adenosine and involved A_1 receptor-dependent depression of the cAMP levels (141). The differential sidedness of the adenosine effect has previously been put forward by a study of IMCD primary culture, showing that apical application of adenosine required much higher concentrations (10^{-4} M) to inhibit the AVP-induced increase cAMP levels in the cells, as compared to basolateral application (maximal effect 10^{-6} M adenosine) (742). This highlights the paracrine nature of the adenosine effect.

In summary, the actions of adenosine on transport in the loop of Henle and the CD are primarily inhibitory with respect to Na^+ and water handling and thus promote a natriuretic and diuretic response. Viewed in conjunction with the effect of ATP via the P2 receptors, the action of ATP and adenosine are synergistic to facilitate volume and Na^+ excretion. This contrasts with the effect of adenosine in the PT, where it acts to increase absorption. It is interesting to consider the net effect of ATP release, which will be the net effect of both P2 and adenosine receptor activation. In TAL, DCT, and CD, the overall effect of P2 and A_1 receptor activation is likely to be transport inhibition, whereas the overall effect for the PT is less clear. One could speculate that these paracrine factors in the proximal tubule outbalance each other, securing a stable PT function regardless of the current challenge. There is currently little doubt that adenosine is a renal paracrine modulator of cell functions as established in several other organ systems. The adenosine concentration in the blood, and thus, in the primary filtrate, is around 60 nM (663). Its precursor ATP is highly abundant in all kidney cells. Hypoxia and other triggers cause

pronounced nucleotide release with marked increases of tissue and urine adenosine as a result of CD73 activity. The nature of adenosine as paracrine factor is nicely demonstrated in the effects of A_1-receptor antagonists in isolated PT without prior addition of adenosine. The marked transport effects in these experiments must indicate that the tissue (PT) constitutively releases adenosine (or a precursor), and receptor inhibition impedes this effect.

P2 receptors in nephron and collecting duct; effect on transport

The Proximal tubule only expresses one functional P2 receptor in the apical membrane; $P2Y_1$ (23), whereas the basolateral membrane contains several P2 receptors ($P2Y_4$, $P2Y_6$) (24, 26, 685). Activation of these receptors has been demonstrated to have clear functional implications. Most strikingly, stimulation of $P2Y_1$ results in inhibition of HCO_3^- absorption (23), which immediately fits the concept of ATP, causing transport inhibition in absorptive epithelia. Moreover, ATP has been shown to stimulate gluconeogenesis in freshly isolated PT from rats (137) and to activate basolateral Cl^- channels in PT form *Necturus maculosus* (57), both effects mediated by P2Y receptors.

Rat thin limb of the loop of Henle expresses functional P2 receptors, with $P2Y_1$ and $P2Y_2$ receptor characteristics (24). Here the $P2Y_1$ seemingly is apically expressed because of a strong mRNA signal in this segment, without any functional evidence for the receptor in the basolateral membrane (24). There is, however, evidence for an equipotent ATP/UTP receptor in the basolateral membrane, which, based on PCR, is likely to be the $P2Y_2$ receptor (24). The potential functional consequence of the receptor expression in this segment has yet to be established.

Functional and molecular P2 receptor expression pattern has been extensively studied in TAL. Both ATP and UTP causes robust $[Ca^{2+}]_i$ responses in cortical TAL (cTAL) (488) and medullary TAL (mTAL) (294). In this segment, the $P2Y_2$ receptor is the only functionally relevant apical P2 receptor, since $[Ca^{2+}]_i$ responses inflicted by both ATP and UTP is completely absent in mTAL isolated from the $P2Y_2$ receptor knock out mouse ($P2Y_2^{-/-}$). The basolateral membrane expresses more functional P2 receptors, and thus, basolateral application of ATP triggers a substantial increase in $[Ca^{2+}]_i$ in mTAL from $P2Y_2^{-/-}$ mice, although the UTP response is completely absent in this preparation. Despite this, activation of the $P2Y_2$ receptor does not influence the transport function in mTAL (401, 402). Interestingly, however, the $P2Y_2$ receptor is essential for the $[Ca^{2+}]_i$ oscillations and interleukin 6 (IL-6) release from the epithelial cells in mTAL that occurs after exposure to the *E. coli* virulence factor α-hemolysin (92). ATP-induced P2 receptor signaling has also been implicated in cellular release of tumor necrosis factor α (TNFα) (254, 343), which recently have been proposed to elicit sizeable inhibitory effects on NKCC2A dependent transport in medullary TAL. (233). This suggests that the $P2Y_2$ receptor in this segment primarily ensures a proper immunologic response to noxious substances.

When applied basolaterally, ATP markedly inhibits the transepithelial transport in mTAL (401, 603), which is mirrored by a simultaneous intracellular alkalization (114). This effect is mediated by P2X receptors, of which the $P2X_4$ has been demonstrated to be a player (401). Thus, overall ATP, upon release, will inhibit the transepithelial transport, which tentatively would reduce the urinary concentration capacity and thus, increase diuresis. It is currently not clear how this transport inhibition is brought about. NO was previously suggested to be the signaling molecule mediating the ATP-induced inhibition of NKCC2 (645). However, data are supporting that the ATP-mediated transport inhibition is Ca^{2+} independent and, thus, does not rely on Ca^{2+} activation of NOS. Moreover, recent data clearly show that inhibition of NOS by other means does not prevent the P2X-dependent transport inhibition in mTAL (645). Please see section 3.2 for the full discussion of these issues. Despite the insecurity regarding the precise mechanism, ATP will, as extracellular signaling molecule, reduce transepithelial transport in this segment.

The number of studies addressing the P2 receptor function in DCT is limited because of the given difficulties in isolating native tissue for functional measurements. Thus, an effect of ATP on transport function has only been demonstrated on cell lines generated from immorto-mice (108). The study by Dai et al. on DCT cells demonstrates a reduced Mg^{2+} uptake after exposure to ATP. These cells also respond to UTP and ADP with a marked increase in $[Ca^{2+}]_I$; however, the inhibition of the Mg^{2+} transport was mediated by a P2X receptor (108).

The collecting duct is currently the only

segment, which proposedly expresses apical P2X receptors (369, 730). In addition, the CD, similar to the other segments, also expresses $P2Y_2$ receptors both in the apical (362) and basolateral membrane (134, 318, 319, 550). In the CCD, ATP applied either to the apical or basolateral side markedly reduces ENaC-dependent Na^+ absorption (103, 362, 662, 730) and K^+ secretion via ROMK (382). The $P2Y_2$ receptor-dependent inhibition of ENaC is mediated via phospholipase C-dependent breakdown of PIP_2 in the inner leaflet of the apical membrane (506, 507) that directly prevents the molecular interaction of PIP_2 with cytosolic domains of ENaC (346, 388, 506). In IMCD, application of ATP to the basolateral side diminishes the aquaporin-2 (AQP2)-dependent water transport (318, 550) and urea transport (764). The effect on water transport is brought about directly by G_i protein-dependent reduction of cAMP (318). Thus, again in this segment, extracellular ATP reduces epithelial transport. This P2-mediated transport inhibition is an overarching theme in all tubular segments of the kidney, and we propose that ATP signaling works as an intrinsic diuretic. By inhibiting epithelial transport, ATP also relieves renal epithelial cells from an O_2 and energy-demanding process. This allows the cells to reserve their energy for homeostasis and self-preservation during either over-stimulation or in response to external noxia.

What triggers nucleotide release in renal tubules? Paracrine signaling is called upon in a number of physiological or pathophysiological situations. In renal purinergic signaling, there are few examples, where at least some of the steps, from the initial stimulus to the resulting paracrine response, have been elucidated. One example is the amplification of subtle mechanical stimuli by purinergic signaling. The primary cilium has been recognized as an organelle that makes cells more susceptible to changes in fluid flow (515) in renal epithelia as well as in numerous other cell types (119, 395) and even in some instances in endothelial cells (5). Bending the primary cilium leads to a substantial Ca^{2+} influx, a subtle signal that is amplified by local ATP release (266, 514, 524, 739). Thus, the downstream cellular events will be dictated by the expression pattern of P2 receptors in the given tissue, and therefore, can explain why the ciliary $[Ca^{2+}]$ signal expands into a global $[Ca^{2+}]_i$ response in some cells and not in others (349). The model of a subtle ciliary response being amplified by paracrine purinergic signaling is appealing in tissues working in a coordinated fashion like renal epithelia. All renal tubular segments express primary cilia, including the parietal layer of Bowman's capsule (14, 356, 500), however, specifically in CNT/CD, it is only the principal cells that exhibit an apical primary cilium (14, 392, 500). There is reasonable consensus about the primary cilium as an important sensitizer for detection of subtle flow changes in cultured cells, where the flow conditions can be controlled and are close to laminar (338-340, 344, 515, 516, 554, 555, 591, 612). Recently, LLC-PK1 cells were demonstrated to show a robust cilium-dependent $[Ca^{2+}]_i$ response, which modulated the endocytotic activity. This effect was abolished and by scavenging extracellular ATP by apyrase or by adding 100 μM ATP extracellularly (524), confirming a secondary paracrine element of subtle mechano-sensation.

There are other membrane structures that have been proposed to sensitize cells to changes in apical flow rates. This particularly includes the microvilli of the CD intercalated cells. The β-intercalated cells express connexin30 (Cx30) in the apical membrane domain (409). This finding implies that Cx30 might form hemichannels in the apical membrane (409), providing an exit path for intracellular ATP to the pre-urine (409, 609). In a model for flow sensing by the intercalated cells, an increase in fluid flow is proposed to be sensed by the intercalated cells, causing ATP release through Cx30, which then results in an autocrine/paracrine mediated $[Ca^{2+}]_i$ increase. The model is supported by studies of flow-induced K^+ secretion mediated by the Ca^{2+} sensitive K^+ channel $K_{Ca}1.1$ (154, 378), which is preferentially expressed in intercalated cells (478, 484). Similar to the cilium-dependent flow response, there are some issues that are not quite settled for this model. Firstly, connexin hemi-channels do not provide selective ATP-release. The assumption that ATP is released through a non-selective, larger pore immediately defies the purpose that extracellular ATP is necessary to inflict K^+ secretion. Opening of connexin hemichannels itself would allow immense efflux of K^+, which in fact would be far more effective for sustained K^+ secretion than a selective K^+ channel. K^+ secretion via a selective K^+ channel would immediately clamp the apical membrane potential to the reversal potential for K^+, and thus, prevent further secretion unless the membrane is depolarized by either Na^+ influx or Cl^- efflux. A connexin hemichannel would

allow influx of Na^+, divalent cations and efflux of anions, and thus, depolarize the membrane, so providing a driving force for constant K^+ secretion, rendering the $K_{Ca}1.1$ redundant.

ATP release in the kidney is not limited to mechanical stimulation. Generally, ATP is released in response to an increase in $[Ca^{2+}]_i$ either via vesicular release (49) or through pannexins or connexin hemichannels (98). In a renal context, it has been demonstrated in perfused mTAL and CCD that both AVP and dDAVP trigger bursts of ATP release measured with biosensor cells (459). This potentially means that many hormonal stimuli would be modified by P2 receptor activation. In this instance, one could speculate that the ATP release protects the cells from overstimulation with AVP and dampens the volume challenge for the cells by reducing the AQP2-induced water permeability.

In addition to physiologically induced ATP release in renal tubules, this is an important issue during various pathological states. ATP release can also be triggered during ascending urinary tract infections. In the case of α-hemolysin (HlyA)-producing uropathogenic *E. coli*, HlyA is in itself as previously mentioned able to insert it into renal epithelial plasma membranes and to cause $[Ca^{2+}]_i$ oscillations and release of IL-6 (92). HlyA inflicts ATP release apparently by letting ATP past the toxin pore (614). Thus, it is not completely surprising that the following $[Ca^{2+}]$ oscillations and IL-6 release require P2 receptor activation (92). Since ATP inhibits transcellular transport in the various renal segments, it has been speculated that this may potentially wash bacteria away from the epithelial surface. Interestingly, pyelonephritis in children is associated with reduced urinary concentration capacity (619), which in turn would fit the inhibition of AQP2-mediated water transport in response to $P2Y_2$ activation (318). Children with pyelonephritis often present with a primary pseudo-hypoaldosteronism, i.e. hyponatremia and reduced renal K^+ secretion (for review see (45)). Obviously, this could have a variety of explanations but does fit the $P2Y_2$ mediated ENaC inhibition. In the mentioned review (45), there is no immediate association to *E. coli* infection; however, a substantial number of urinary tract infections are caused by *E. coli,* and thus, it is at least conceivable that the urinary concentration defects and the pseudo-hypoaldosteronism are caused by HlyA-mediated ATP release and tubular $P2Y_2$ receptor activation. Moreover, nucleotides are always released during severe acute renal damage. This includes not only ATP but also its derivatives and other P2 receptor agonists like UTP/UDP and UDP-glucose. Interestingly, the UDP-glucose sensitive $P2Y_{14}$ receptor is highly expressed on CD intercalated cells. Activation of this receptor causes release of cytokines such as keratinocyte chemotactic factor (the murine cytokine that activates IL-8 receptors), MIP-2a, and MCP1 from the intercalated cells via the ERK pathway (20). The study suggests that the intercalated cells are central in inflicting renal inflammation via activation of the $P2Y_{14}$ receptor. All these examples illustrate the diversity of situations where renal cells are exposed to increased concentrations of nucleotides that influence the local epithelial transport, the constriction level of the surrounding vessels, and potentially the degree of tissue inflammation.

Collectively, purinergic signaling, in general, causes transport inhibition in the tubular segments. Thus, this signaling system is a prototype of a reno-protective system that causes a combination of vasoconstriction and inhibition of renal tubular transport of NaCl and water.

3.2 Nitric oxide signaling by the renal tubules

Many paracrine factors, which have been characterized as signaling molecules in the vascular system, were also suspected of having physiological relevance for renal epithelia. This certainly also applies to NO, which, as mentioned, is the main component of the classical endothelium-dependent EDRF response. Determining the exact physiological role of NO is technically challenging because NO, like many other paracrine signaling molecules, is difficult to detect directly. Generation of NO can, as one option, be determined by electrodes (112) or via NO sensitive fluorescent probes. The electrodes are the gold standard but are still rather bulky, and thus, require larger tissue preparations. Often the scientific questions require discrimination of NO generation and signaling on the single-cell level where electrodes cannot provide adequate data acquisition. Therefore, fluorescent probes are used extensively despite that these are single wavelength probes reporting cumulative NO formation (413) as opposed to the NO-electrodes ability to detect dynamic changes in NO. Both methods have drawbacks in terms of competing nitrogen-compounds. This calls for caution with the interpretation of the data and usually requires substantiation by several methods.

NO-signaling in the proximal tubule. NO-signaling has been suggested to influence epithelial transport in practically all renal tubular segments. The PT has been demonstrated to primarily express inducible NO synthase (iNOS/ NOS2) (400, 658), and thus, NO has been implied to play an immune-modulatory role in this segment (411). This fits well with the demonstration of a rather low NOS activity in PT as compared to other tubular segments (626). In line with this, NO production is markedly stimulated by lipopolysaccharide (LPS) in cultured PT cells (136, 412, 667, 681). However, NO-production has also been shown to be stimulated by classical transport regulating hormones such as atrial natriuretic peptide (ANP) and AngII (412), which qualifies NO as a possible modulator of tubular transport. Early studies have demonstrated that after imposing a systemic volume increase, inhibition of NO synthesis reduces the fractional excretion of Li^+ (10), which indicates that Na^+ reabsorption is reduced by NO somewhere along the tubular system. The effect of NO on transepithelial transport in PT is, unfortunately, somewhat controversial. Initially, it was reported that stimulation of NO production or application of NO donors reduced the overall Na^+/K^+ pump (226, 373) and Na^+/H^+-exchange activity (544), reducing the overall fluid reabsorption (144, 736). Moreover, it was shown that NO also diminished PO_4^{3-} reabsorption in PT by reducing the apical abundance of NaPi-IIa (21) and the multidrug resistance protein (MRp2)-mediated transport (449). Therefore, it was a surprise when Wang found a completely opposite effect of NO on Na^+ and HCO_3^- reabsorption in isolated rat PT (709). These data were substantiated, both in a follow-up study from the same laboratory investigating NOS-deficient mice, which indeed show reduced fluid and HCO_3^- reabsorption in microperfused PT (710) and by Amorena and Castro demonstrating an increased H^+ secretion to the lumen in response to increased intracellular cGMP and NO (12). Notably, PT fluid and HCO_3^- reabsorption was markedly lower in nNOS *knockout* mice and essentially unchanged in iNOS *knockout* mice. This suggests that nNOS is expressed in PT and that iNOS even though present, has little influence on transport regulation under normal circumstances. It should, however, be mentioned that a study by Vallon et al. showed increased fractional reabsorption of fluid and Cl^- in PT of nNOS deficient mice (689), which is not immediately compatible with the studies on isolated perfused PT. These discrepancies may partially reflect variation in the concentrations of the NO-donors and inhibitors at the site of action. Interestingly, NO has been reported to show dual, concentration-dependent effects in a study of the basolateral the K^+ channel Kir6.1 (61, 432), where low concentrations of NO donors stimulate the channel, whereas high concentrations of NO donors inhibit channel activity (432). Interestingly, NO has been shown to reduce the activity of ecto-5'-nucleotidase (596), which will result in reduced adenosine generation and potential accumulation of ATP and ADP in the extracellular micro-milieu. Because ATP is known to reduce the proximal tubule Na^+ and HCO_3^- reabsorption (23, 709), this effect may have added to the diversity of the results of NO in PT transport.

In summary, the overall effect of NO in the PT is a stimulation of transepithelial Na^+ transport – a conclusion that duly weighs the impact of cell culture results against result from isolated tissue and micro-perfusion studies. This effect is, however, likely to be modulated via competing paracrine factors. Thus, it is interesting that NO production is stimulated by LPS from *E. coli* (136, 302, 412, 667, 681) and that the NO production is associated with increased cell damage (302). The notion that NO production may result in acute cell damage in PT has been supported by *in vivo* studies. One suggests that acute exposure to iv LPS triggers NO production and, subsequently, acute proximal tubular damage in humans (249), whereas others show acute proximal tubular cell death and natriuresis upon sustained NO inhalation in pigs (212) and NO-dependence of macrophage induces PT cell death (316). However, there is no consensus on the matter, regarding a decisive role of NO to trigger PT cell injury or its role in acute renal injury following liver insufficiency (694).

NO signaling in thick ascending limb. Similar to proximal tubule, NO has been suggested as a direct regulator of the transepithelial transport in TAL. All NOS variants have been detected in rat TAL on protein level (167). However, iNOS is not only expressed (9, 420, 425) but has similarly to PT been demonstrated to exhibit some baseline NO production (626). Again, for this segment, there have been diverse data on NO's effect on tubular transport. Shortly, TAL supports the overall renal Na^+ and Cl^- reabsorption, which because of the segment's low water permeability, creates the active component of the high interstitial osmolarity in the renal medulla and thus, is essential to the urinary

concentration mechanism. TAL transport is fueled by the activity of the basolateral Na^+/K^+-ATPase creating the driving force for the electroneutral NKCC2. Cl^- leaves to the basolateral side through ClC_{KB} in humans (608) and ClC_{K1} and CLC_{K2} in mice, where ClC_{K1} is predominately localized in TAL (330). Part of the reabsorbed K^+ recycles back to the lumen (19, 32) via ROMK (174, 259, 712, 769). Basolateral K^+ channels are important for the continued Na^+/K^+-ATPase activity and for creating the driving force for Cl^- exit. In terms of K^+ channels, NO has been shown to activate apical ROMK channels (384), which is consistent with transport activation upon increased endogenous NO production.

In the TAL, most publications favor an inhibitory effect of NO on transepithelial transport. The NO-donor spermine NONOate was shown to reduce the Na^+/H^+ exchange activity in mTAL (192), which is consistent with an inhibition of the transepithelial bicarbonate reabsorption. This effect on bicarbonate reabsorption was confirmed by direct measurements of HCO_3^- flux in isolated mTAL using L-arginine and 5-BR-cGMP (469). Similar results were presented for Cl^- reabsorption in this segment, where L-arginine and spermine NONOate inhibited the Cl^- flux in isolated perfused mTAL (504, 505) apparently again through activation of cGMP-stimulated phosphodiesterase (471). Interestingly, the inhibitory effect of L-arginine on the Cl^- flux was abolished in eNOS deficient mice, unaltered in iNOS deficient mice (504), and rescued by expression of eNOS specifically in the TAL of eNOS deficient mice (475). This means that there is also functional evidence for eNOS in TAL (687). Interestingly, eNOS has been shown to exhibit subcellular translocation and phosphorylation in response to changes in luminal fluid flow (473, 474), which emphasize that the relative contribution of the various NOS isoforms may change in response to different stimuli (360, 473, 474). Based on these data, one would expect that anything increasing cGMP would have a similar effect on tubular transport as NO. Thus, in support of NO-mediated transport inhibition in TAL, Néant et al. showed that platelet-activating factor inhibits Cl^- reabsorption in a cGMP-dependent manner (439). That said, it is worth to notice that although NOS activity is usually stimulated by increases in $[Ca^{2+}]_i$., in TAL increasing $[Ca^{2+}]_i$ does not alter baseline Na^+ and Cl^- transport (123). This was demonstrated in mTAL and cTAL from rats and in mTAL from mice by stimulation of the Ca^{2+}-sensing receptor (CaSR), which inflicted a clear transient increase in $[Ca^{2+}]_i$ (123). This CaSR-induced $[Ca^{2+}]_i$ increase did, however, not transpose into an effect on the transepithelial voltage neither at baseline nor after AVP stimulation (123). In support, it was just recently demonstrated that the ATP-induced reduction of transepithelial voltage in mTAL is entirely unaffected by omission of basolateral Ca^{2+} even though this procedure is known to largely abolish the $[Ca^{2+}]_i$ response to ATP applied from the basolateral side (294). Hence, these data clearly demonstrate that $[Ca^{2+}]_i$ has little impact on transepithelial transport. In this context, one peculiarity is that NO production in TAL, supported through eNOS, is increased upon P2X receptor activation (401). P2X receptor activation on the basolateral side is known to reduce transepithelial transport (401, 603). The most straightforward explanation is that P2X activation increases NO production, which in turn inhibits NKCC2, a notion supported by L-NAME in higher concentration completely abolish the effect of ATP on tubular transport (603). However, it must be stressed that the P2X dependent reduction in transepithelial transport cannot be mimicked by P2Y receptor activation, which is known to cause a marked increase in the $[Ca^{2+}]_i$ (401). This supports the previously mentioned finding that increases in $[Ca^{2+}]_i$ do not alter TAL transport, and thus, the P2X receptor-mediated transport inhibition is not supported by Ca^{2+}-dependent NO production. This notion was recently substantiated by a study showing that inhibition of NO production via L-NAME, even in high concentrations, did not influence ATP-induced transport inhibition in mTAL (645). Therefore, there is, at present, very little support for the P2X receptor transport inhibition in TAL being mediated by NO.

Some of the discrepancies between the earlier and the newer studies may be found in the methods used as a measure of transepithelial transport. The most direct quantifiable measure of transport is collection of tubular fluid and determination of the change in fluid composition. Measuring the transepithelial potential difference, the current and the derived resistance clearly is a precise measure of the electrogenic transport but just as clearly cannot determine net electroneutral transport. This method has, however, been key in many important investigations of NKCC2's role in the transepithelial transport of Na^+ and Cl^- and has, thus, proven to be a very accurate readout for e.g. the furosemide sensitive transport. Measurements of the O_2-consumption is a derivative of the transport

function, and one can rightfully assume that most of the energy consumption of the cells reflect transepithelial transport. The O_2 consumption will, thus, indirectly be a measure of both electrogenic and electroneutral transport. In terms of O_2 consumption, it is critical that NO is known to inhibit mitochondrial function (for review see (65)). Generally, NO-donors (499) or deficiency of iNOS results in increased expression of uncoupling protein 1 (UCP1), and thus, affects the oxygen consumption. These results originate from studies on brown fat, but NO has also been shown to regulate UCP2 expression in rat cardiomyocytes (429). UCP2 is expressed in PT and mTAL (170), where the expression level both in cortex and medulla is related to non-transport connected oxygen consumption (171, 482, 483). Therefore, these indirect measures of transepithelial transport must always be weighed for the given application. With the strength and weaknesses of the various methods, it is not surprising that results do not always match entirely. Despite the inconsistencies, which need to be resolved in terms of signal transduction, the majority of the literature presents data supporting NO mediating transport inhibition in this segment.

NO-signaling in macula densa. Macula densa cells have early been identified as the prime site for nNOS (NOS1) expression (428, 671, 728). The principal function of this specialized cell cluster is as mentioned to sense the intratubular Cl^- concentration serving the TGF (see section 2.2). Since NOS expression in these cells is much higher than in other renal epithelial cell types (428), clearly this must have a functional implication. Initially, there was support for constitutively active nNOS, which supplied NO to dilate the afferent arteriole and dampen the TGF mechanism and thus, keeping GFR at a stable higher level (665, 728). In support of this notion, nNOS knockout mice exhibit a lower single nephron GFR – a phenotype that could be overruled by removing Na^+ and Cl^- delivery to macula densa (689). These findings are compatible with NO-dependent transport inhibition at the macula densa, which is equivalent to low Na and Cl^- delivery to the area, and thus, would cause vasodilation of the afferent arteriole and increased GFR. The concept of NO inflicting transport inhibition in macula densa is backed up by various studies showing NO-mediated activation of either guanylate cyclase or inhibition of cGMP-dependent protein kinase (534). It must be noted that NO-mediated transport inhibition in macula densa, indirectly support an inhibitory effect of NO in TAL because of the similarity of the transport machinery in the two segments.

NO-signaling in collecting duct. In the CD, there is substantial literature concerning the effect of NO on transepithelial transport. Again there is significant diversity with regard to the direction and even presence of the effect. This segment has the highest total NOS activity of all renal tubular segments (735) and expresses nNOS in principal cells (713) and iNOS in intercalated cells (9, 672). The differential water permeability of this segment is regulated by cAMP, where an increase in cAMP enables insertion of AQP2 into the apical membrane of the CD principal cells (628). However, a cGMP-mediated effect on water transport has not reached consensus. ANP produces substantial natriuresis (60, 113), an effect that has been demonstrated to require cGMP as second messenger both in the CD and for its vasodilator effects (267, 446, 460, 633, 682, 733). The effect of ANP on water transport is of interest to the NO signaling field because of the common second messenger. Based on the overall effects of ANP on the diuresis, one would assume that ANP would reduce the water permeability and transport in CD. Several studies support this notion, demonstrating that both ANP and cGMP reduce the AVP-induced CD water transport (543) and that NO donors as spermine NONOate or nitroglycerin reduce the AVP-induced water transport in isolated CCD from rats (187).

Contradictory to these findings, it was shown that NO in a cGMP-dependent manner increases insertion of AQP2 into the apical membrane in rat kidney slices and LLC-PK1 cells (55). These findings were supported by a number of studies using sildenafil citrate, which increases the intracellular cGMP levels and also enhances the membrane abundance of AQP2 in AQP2 expressing in LLC-PK1 cells, in rat IMCD (56) and mouse CCD cells (53). Moreover, sildenafil was shown to reduce polyuria and increase apical targeting of AQP2 in rats with lithium-induced nephrogenic diabetes insipidus (564). To further blur the picture, some studies do not support cGMP-mediated effects on water transport. One study failed to detect any effect of NO on either the basal or AVP-induced water transport in rat IMCDs despite a substantial increase in cGMP in response to NO (773). This was partially supported by data on water permeability measured indirectly as cell swelling of IMCD cells, which did not show any acute alterations in response to ANP but did exhibit reduced AVP-induced water

permeability after co-exposure to ANP and NO-donors (326). Moreover, NO had no measurable effect either on the basal or AVP-induced urea and water permeability in IMCD despite a pronounced effect on the cGMP production in the same tissue (773). These data support the notion of a limited effect of NO on water transport. Thus, similar to the PT, the compiled data draws a muddy picture of the role of NO signaling in CD water transport. This may indicate that NO is not a very pronounced player in the regulation of tubular transport, or it could reflect we lack essential factors that have not been accounted for in the conducted studies. However, it must be emphasized that there has been observed gender difference in terms of NO's effect on water handling in the CD. In mice deficient of NOX3 specifically in the CD, it was clear that male $NOX3^{-/-}$ mice were not able to dilute the urine to the same degree as the wild type when exposed to 7 days of volume load, whereas this was not the case in females (185). Thus, one possible explanation for the variable results in this segment could be that the NO-dependent inhibition of water transport is observed in males only.

Regarding NO's potential effects on Na^+ reabsorption in CD, one critical question is the role of cGMP. Similar to water transport, inspiration was taken from studies using ANP. From the systemic effects of ANP, one would anticipate that ANP reduces the transepithelial Na^+ reabsorption in CD. Compliant with that notion, ANP was shown to inhibit Na^+ and Cl^- reabsorption in isolated perfused rat CCD (447). These findings were, however, not consistently confirmed by consecutive studies in the same preparation (241, 549). In fact, the absence of effect of ANP on Na^+ reabsorption was reported in other studies. In cells derived from mouse CCD (M1), the baseline transepithelial transport was unaltered by cGMP in (634), and addition of ANP did not change Na^+ transport in stop flow experiments of the rabbit CD (165). Moreover, increasing the intracellular cGMP did not influence the electrogenic transport in principal cells in a patch-clamp study on isolated rat CCD (572). This conclusion was based on that neither ANP, BNP, urodilatin, guanylin, uroguanylin, or dibutyryl guanosine 3',5'-cyclic monophosphate had any effect on either the membrane potential or the lumen to bath Na^+ flux (572). Collectively, the data exclude a major effect of ANP and cGMP on CD transepithelial Na^+ transport.

Despite the discouraging data on ANP/cGMP, there has been keen interest in defining the effects of NO on CD Na^+ reabsorption. Initially, NO was shown to inhibit the transepithelial Na^+ transport through an effect on apical ENaC in cultured mouse CD cells (635) and isolated perfused tubules from rats (636). These experiments have later been confirmed in patch-clamp studies in split open CD from mice (273). The transport inhibitory effect of NO is further supported indirectly by a study of Cl^- transport, which found that NO donors reduced, and NOS inhibition significantly increased the Cl^- transport in CCD in a benzamil sensitive way (492). The authors conclude that the inhibition of Cl^- transport is secondary to NO-mediated inhibition of ENaC (492). Somewhat conflicting results come from rat split open tubules (635, 636), where the open state probability of ENaC was reduced after addition of L-NAME and two NO donors (S-nitroso-N-acetyl penicillamine and sodium nitroprusside) could reverse this effect (381). This effect was, however, not mimicked by 8-bromo-cGMP on excised patches and data support that NO's effect was a result of hyperpolarization provided via activation of basolateral K^+ channels (258, 380, 383). Thus, the compiled evidence defines NO as an inhibitor of CD Na^+ transport without any significant effect on water transport.

Trigger for NO increase in renal tubules. The stimuli that have been identified to release NO from renal epithelial cells can be grouped into categories. The first is G-protein coupled receptors, including systemic hormones or local paracrine factors. NO production has been suggested to increase in IMCD from mice in response to AVP (424). Apparently, the increase in intracellular NO is a consequence of a vasopressin-induced increase in $[Ca^{2+}]_i$ (424) and required V_2 receptor activation (456). Similarly, ATP has via P2 receptor-activation been shown to trigger NO generation in TAL (74) and CD (637). It must, however, been considered that NO production in these studies was measured only as a cumulative response of the single wavelength probe DAF-2 (424, 456). The second category of stimuli for NO production is mechanical perturbation. Shear stress has been proposed to increase NO production in IMCD cells (75) and in TAL, where NO has been suggested to act distally to endothelin in a negative feedback loop that reduced Na^+ reabsorption in response to shear stress (273). However, in TAL, the mechanically induced NO release is very likely to be secondary to flow-induced ATP release (74).

Interestingly, TAL has extensive extracellular and intracellular carbonic anhydrase

activity. As mentioned earlier, the carbonic anhydrase (CA II) is one of the many enzymes, which can catalyze NO production, most likely by nitrous anhydrase activity (1). The TAL expresses both a cytosolic (CA II) (625) and a luminally facing carbonic anhydrase (CA IV) (64). The nitrous anhydrase activity of CA II is most prominent at lower pH (5.9) compared to pH 7.2 (1). Since the urine pH in TAL is around 6.7 (131), and the nitrous anhydrase activity is preserved for CA IV, NO could potentially be generated from nitrite in the urine (~3.7 μM)(684). This may possibly be a third category of NO source in renal epithelia. Finally, endothelial production of NO may potentially also serve as a source of NO affecting the tubular function. As mentioned earlier, pericytes surrounding the descending vasa recta have been demonstrated to be sensitive to NO (77, 99, 138) in response to classical EDRF endothelial NO generation (77). This essentially means that shear stress-induced NO release from the endothelial in descending vasa recta potentially could inhibit the transepithelial transport in TAL and thereby relieve the segment from overstimulation.

Taken together, NO increases transport in PT but predominantly inhibits transport in all the tubules distal from this segment. However, it is puzzling that NO stimulates bicarbonate reabsorption in PT but inhibits it in TAL even though the cellular mechanism for bicarbonate reabsorption is identic in the two segments. So clearly, there are some issues that will need further consideration. Since NO in most segments reduces the renal transport, one would expect it to protect the renal segments distal to PT. However, there is currently very little data outside the PT on whether NO-generation influence comprised tubular function, tubular death, or cellular dedifferentiation.

3.3 Local peptides as a tubular signaling molecule - angiotensin II- intrarenal RAAS, endothelin, and bradykinin

The tubular renin/angiotensin system

RAAS is a central feedback-regulated hormonal system to control Na^+ and K^+ homeostasis and systemic blood pressure. The plasma concentration of the enzyme renin is tightly controlled by (1) the relative stretch of the afferent arteriole, (2) the Cl^- concentration in the pre-urine at the macula densa, and (3) by the sympathetic tone resulting in direct β_1 stimulation of the JG cells. These tree sensing systems continuously monitor the body's volume status and blood pressure and assure adequate compensation by systemic vasoconstriction and increased Na^+ absorption to the bloodstream from the AngII and aldosterone sensitive epithelia.

Over the last decades, RAS, in addition to its systemic effect, has been promoted as an autocrine/paracrine system within the kidney. Here one of the A's is omitted because aldosterone is not produced locally in the kidney, and thus, is not a paracrine signaling element. Collectively, there is evidence that at least some of the other components of RAS are locally produced in the kidney (see Fig. 4). However, despite local production of angiotensinogen, demonstrated with *in situ* hybridization (278), it is now well established that the liver is the main source for the angiotensinogen found at least in the murine kidney (404). Similarly, most of the components for the RAS are actually filtered and therefore mirror the systemic production and regulation of RAS components (546). Under physiological situations with an intact filtration barrier, angiotensinogen is, despite its size, apparently filtered and taken up from the pre-urine via megalin-mediated endocytosis in PT (404, 509). This uptake can easily explain previous immunohistochemistry demonstration of angiotensinogen in PT (538).

In addition, the data regarding megalin-dependent uptake of angiotensinogen suggest that angiotensinogen is unlikely to be present in relevant amounts in the renal tubular systems distal to PT, which has also been confirmed experimentally (546). A natural consequence of this is that angiotensinogen has to be further processed by the PT, for RAS to be able to influence renal epithelial transport in a paracrine manner. The kidney does express renin in other places than in the JG cells. This expression is, however, first substantial very late in the renal tubular system, in the principal cells of the connecting tubule (545) and can therefore not support the conversion of angiotensinogen to AngI in PT. Both pro-renin and renin are filtered with a sieving coefficient around 0.01-0.02 (546), and filtered renin is similar to angiotensinogen taken up by the PT (50) in a megalin-depended manner (509). The endocytosis of angiotensinogen and renin could, in principle support, AngI production in the PT lysosomes. The further conversion of AngI to AngII can readily occur in the PT since angiotensin-converting enzyme (ACE) is expressed in the PT to

a larger extent compared to other tubular segments (81). Regarding ACE, ACE2 that converts AngII to Ang1-7 is also heavily expressed in the kidney (129), particularly in the brush border of PT (363), which allows Ang1-7 to be detected in the urine (738). Ang1-7 has been suggested to inhibit Na^+ reabsorption in PT in higher concentrations via stimulation of phospholipase A_2 (13), whereas Ang1-7 stimulate PT transport at more physiological concentrations (186). There is very little further support for an effect of Ang1-7 on epithelial transport and will, thus, not be further considered here.

Collectively, these discoveries regarding the renal RAS puts a question mark after whether the renal RAS is genuinely a local paracrine system or whether it should still be regarded as a systemic hormonal system. Undoubtedly, the renal tubules do express specific receptors for AngII, i.e., AT_1 and AT_2, where the AT_1 receptors are further divided into AT_{1a} and $AT_{1b.}$ Generally, AT_1 receptors are expressed in vascular smooth muscle cells, the mesangial cells in the glomerulus, to a low degree in PT, in TAL, macula densa, and DCT/CD (237, 491). From binding studies, it has been determined that AngII binds equally to the PT apical and basolateral membrane (66, 67). Based on this, it was concluded that there must be a higher absolute number in the luminal membrane because of the larger apical surface area in PT (66, 67). There is currently not complete consensus regarding their relative expression of AT_1subtypes or expression of AT_2 receptors in PT (263, 523). Surprisingly, the AT_1 receptor is also functionally relevant for internalizing circulating AngII into PT cells, as demonstrated both in rats (776) and using AT_{1A} receptor KO mice (372). Apparently, AngII from the plasma is taken up by endocytosis of ANGII bound to the AT_1 receptor, since inhibition of AT_1 receptors blunts the accumulation of ^{125}I-angII in this tissue (692), although this uptake accounts for a minor part of the AngII in PT.

The described tubular uptake of filtered precursors and enzymes creates a basis for local conversion of AngII for modification of tubular transport. Apparently, this mechanism allows the content of AngII to be up to 500 times higher in kidney tissue than the arteries of pigs (691). Moreover, any AngII present in the lumen of PT is rapidly broken down and reabsorbed into the proximal tubular cells (497), which supports the notion that AngII is a critical local signaling molecule. Taken together, AngII is present in the environment of the renal tubules expressing the relevant receptors and an AngII degradation system that can terminate the signal. The remaining questions are (1) what does AngII do with regard to renal transport? (2) which receptor subtype is responsible for the functional effect of AngII? – (3), and how is the AngII response regulated?

AngII has been demonstrated to have a bimodal effect on volume reabsorption in PT. At physiological concentrations, basolaterally applied AngII markedly stimulates the volume reabsorption in an electroneutral manner, whereas high concentrations of AngII (10^{-7} M) inhibit of PT epithelial transport (584). The stimulation of the overall PT transepithelial transport is a consequence of stimulation of multiple PT transporter proteins, namely NHE_3 via a PKC mediated reduction in cAMP (375-377), vacuolar H^+-ATPase activity (700), Na^+-HCO_3^- cotransport (197), Na^+-glucose transport (191) and the Na^+/K^+-ATPase activity (190). Moreover, long-term application of AngII increases the overall expression level of NHE_3 (126) and thereby further enhances the capacity of $NaHCO_3$ transport. In addition to tubular transport, AngII has also been demonstrated to increase the production and secretion rate of NH_4^+ (430, 431), and thus, expand the renal capacity for acid excretion. The bimodality of AngII is not only reflected in HCO_3^- reabsorption but also seen in the NH_4^+ -production, with stimulation at low concentrations (10^{-11}-10^{-9} M) whereas a high concentration inhibits NH_4^+ -production (265). At least for the HCO_3^- reabsorption, the effect of AngII in low concentration on PT transport is mediated via a reduction of cAMP and reduced PKA activation (375) possibly via PKC (168, 571). In contrast, the inhibition of PT transport by higher concentrations of AngII seems to result from inhibition of basolateral Na^+-HCO_3^- cotransport (97). Concerning the functional receptor subtype, the bimodal nature of the AngII strongly suggests the presence of two receptor subtypes, with different sensitivity to AngII. However, data from AT_1 receptor KO mice show that these mice lack the stimulatory action of low concentrations of AngII on the HCO_3^- reabsorption, but also lost the inhibitory effect at high concentrations in PT (263, 768).

As mentioned, AT_1 receptors are expressed along the entire nephron and collecting duct, and thus, it is not surprising that AngII has effects on transport distal from the PT. Accordingly, it has been possible to detect AngII-induced effects in practically all tubular segments distal to PT.

Systemically applied AngII in doses that do not change the blood pressure also elevates the protein expression levels NKCC2 in cTAL, the Na^+-Cl^--cotransporter (NCC) in DCT and various ENaC subunits in the CCD (444). In rat DCT, AngII has also been demonstrated acutely stimulate NCC activity via the WNK4/SPAK activation and thus, increases NCC phosphorylation (563), promoting NCC trafficking to the apical membrane (565). All these changes should collectively increase DCT Na^+ reabsorption, which has also been demonstrated after chronic infusion with AngII in mice (765). Regarding the AngII-induced effect on Na^+ reabsorption of CD, AngII has also been shown to stimulate ENaC-mediated Na^+ reabsorption in isolated CCD from mice and rats in a PKC-dependent way (396, 644), although it must be noted that Mamenko et al. could not confirm an AngII induced Ca^{2+} response in split open mouse CCD (396). In addition to the effect on Na^+ transport, AngII has been demonstrated to inhibit the H^+-ATPase activity on α-intercalated cells of rat CD (673). Taken together, AngII potentiates the effect of high circulating aldosterone levels and assists in Na^+ preservation in the body.

In addition to the conventional RAAS, prorenin has also been suggested as a paracrine factor in renal tubular signaling (Fig. 4). Moreover, the prorenin/renin receptor (PRR)-signaling has been demonstrated to be essential for a normal tubular formation and kidney development (621, 622). As mentioned, prorenin is filtered in the glomerulus (546), which potentially allows it to work as a systemically produced signaling molecule for modifying the tubular function from the apical side. Moreover, PRR has recently has been demonstrated functionally to be localized in the macula densa (541), where it through MAPK ERK1/2 induced COX_2 stimulation, and PGE_2 release increases renin release from the JG cells (541). However, renin is, as mentioned, also produced by principal cells of the connecting tubule (545) and, thus, likely to inflict local effects within this segment. The renin/prorenin receptor (PRR) has been cloned (443) and interestingly, it is most expressed in the kidney in α-intercalated cells of the CCD (751). This finding implies a true paracrine effect of prorenin release from the principal cells inflicting actions in the neighboring intercalated cells. Deficiency in PRR results in embryonic lethality in mice (598), most likely as a result of the receptor's regulation of the V-ATPase (ATP6AP2) (102). However, CD specific PPR knock out mice have a striking phenotype, with reduced kidney size, renal function, and hypotension (519). Interestingly, the CD-$PPR^{-/-}$ showed reduced abundance of cleaved αENaC and γENaC alongside an increased urine volume when the mice were exposed to a NaCl load (519) or water load (526). These findings are in line with data showing that renin and prorenin increase ENaC activity in a CD cell culture model (385). Interestingly, there is evidence for interaction between the prorenin signaling and the endothelin system, where the CD-$PPR^{-/-}$ mice shows a marked enhanced urinary ET-1 excretion and reduced, increased abundance of ET_A but reduced expression of ET_B (526).

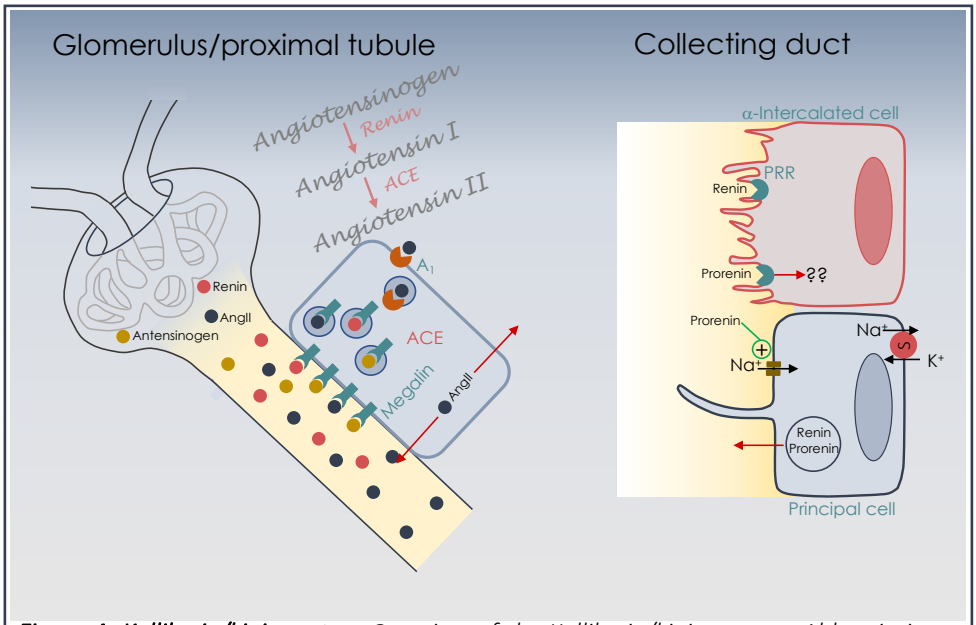

Figure 4 -Kallikrein/kinin system *Overview of the Kallikrein/kinin system. Abbreviations: ACE (Angiotensin converting enzyme), B_1-B_2 (bradykinin receptor 1 and 2), HMWK (high molecular weight kininogen)*

Overall, one can conclude that some elements of the RAAS are afoot as signaling molecules for adaption of the tubular transport. It is unlikely that AngII is a true paracrine signaling molecule. Instead, the AngII that

affects the renal tubular transport appears to be an echo of the circulating AngII levels. The only true paracrine signaling molecule of the RAS is prorenin/renin that in the systemic RAS primarily is a rate-limiting enzyme. However, specifically in the CD, prorenin appears to be an important modulator of tubular transport. Interestingly, both AngII and prorenin/renin in terms of their action are distinct from the majority of the other paracrine factors within the kidney and likely to be a part of the systemic regulation of the circulatory volume rather a local reno-protective signaling system.

Endothelin

Endothelin was initially described as an endothelial-derived autocrine/paracrine factor for modifying the vascular smooth muscle cell contraction. However, the inner medulla of the kidney has been demonstrated to be the primary site for synthesis of endothelin (322). It was initially found to be almost exclusively expressed in the inner medulla CD, although later results demonstrate that ET-1 was produced in lesser amounts by several segments of the renal tubular system (686), including the epithelial cells of the glomerulus (106). The relative production of ET-1 by the respective renal tubular segments is nicely illustrated in an earlier review from Prof. Kohan (332). Of the family of endothelins, ET-1 has been found to be the primary renal isoform. Human ET-1 is produced as a 212 amino acid long prepropeptide, which is sequentially cleaved into the 21 amino acid long ET-1. The pro-peptide can both be cleaved before and after secretion by either of the metalloproteases, ET-1 converting enzyme (ECE-1) or ECE-2 (151, 740), where ECE-2 is mainly responsible for the intracellular conversion to ET-1. Interestingly, Johnström et al. found that the injected [^{18}F]-pro-ET-1 was excreted in the urine without conversion to ET-1 (298), which suggests a relatively low extracellular conversion of pro-ET-1 by the kidney. A few studies have indicated that at least in smooth muscle cells, ET-1 is at least partially stored in cytosolic vesicles, including the Weible-Palade bodies (150, 559, 647). The issue of storage is less well-defined in renal epithelial cells, and thus, the secretory mechanism is not yet settled for the tubular system.

Consistent with the data on renal ET-1 production, the kidney primarily binds ET-1 in the inner medulla (678). The ET-1R has been demonstrated to be widely expressed in the kidney by a binding assay, and the expression pattern essentially matches the production of ET-1. This implicates that ET-1 is a very local paracrine signaling factor. Thus, in addition to the vasculature, including the glomeruli, the ET-1 receptors are primarily expressed in CD (118, 753) with emphasis on IMCD. Functional studies indicate that the ET-1 response in IMCD is mainly inflicted through activation of ET_B receptors (91, 308, 653, 657), a notion backed up by binding studies and mRNA expression. Regarding activation, the ET receptors are all G-protein-coupled, and ET-1 has been demonstrated to increase $[Ca^{2+}]_i$ via IP_3-dependent store release (337, 348) and simultaneous activation of PKC (677) in CD/CD cells. Interestingly, ET-1 elicits relatively prolonged effects for a peptide. The reason is that ET-1's essentially binds irreversibly to the receptor, without apparent desensitization and the receptor-ET-1 complex continues to stimulate the cell even after it is internalized (93).

We consistently ask whether signaling molecules are true paracrine gameplayers in the kidney. This requires, as previously mentioned that the given substance is produced and released by the kidney, express specific functional receptor in the kidney and has a relevant degradation system to terminate the signal. Endothelin, thus, lives up to all these criteria, although the degradation of endothelin is not confined to only one enzyme. In the kidney, endothelin is apparently degraded by numerous enzymes including non-metalloproteases and metalloproteases, (121, 122), enkephalinase-related protease, (135), neutral endopeptidase (615), and a lysosomal protective protein (288), where the relative contribution to ET-1 degradation is undetermined. In addition, we ask whether the system is primarily local. This criterium is fully met for the endothelin system, where practically none of the plasma endothelin can be detected in the urine (2), and thus, the ET that is detected must originate from the renal epithelial cells directly. Moreover, all the components of the full endothelinergic signaling system are present in CD, where the most pronounced effects of the ET-1 resides.

The notion that ET-1 has a vascular-independent effect on the kidney was founded on data showing that despite the ET-1-induced reduction of RBF and GFR, rodents showed increased urine production (22) and reduced urine osmolality (206). Considering the described functional effects, it may not be surprising that ET-1 shares overall effects with ATP/UTP working on P2Y receptors and inhibit the overall water and electrolyte transport in CD. Regarding water

reabsorption, ET-1 markedly reduces the AVP-dependent water-permeability in rat CCD (461, 678). This effect is mediated by a reduction of the cytosolic AVP-dependent cAMP accumulation (676) by a PKC dependent mechanism (678). Concerning the electrolytes, ET-1 has been demonstrated to reduce both the Na^+/K^+-ATPase (757) and ENaC (69, 181, 348) and thus, Na^+ reabsorption in the CD. This transport inhibition directly translates into a salt-retaining phenotype of the CD-specific ET-1 knockout mouse (574). These overall effects amount to a reduction of the transepithelial transport in the CD in response to locally released ET-1. It must be noted that there is a substantial difference in the phenotype in male and female mice in terms of ET-1 signaling. In rats, the ET-1-induced natriuresis is only observed in females (433). The difference is caused by a marked reduction in inner medullary blood flow in males compared to females and is a result of different ET_B receptor signaling, a difference that was eliminated after removal of the gonads (433). In this context, it may be relevant that the individual response to AVP also differs between male and female rats, the females being less sensitive with lower receptor abundance and lower cAMP response (715). Collectively, females are more prone to excrete salt and water load and thus, potentially could be better protected against overstimulation of the collecting duct cells.

The physiological effects of ET-1 are thus, primarily impacting the segment of the largest ET-1 production and ET_B receptor expression. Nevertheless, ET-1 has also been shown to have functional implications in other segments, even though the overall effects lack clarity. In PT, the effect of ET-1 is uncertain. ET-1 has been shown to inhibit bicarbonate transport in rat PT through inhibition of the basolateral Na^+/K^+-pump (189). This finding has been challenged by studies in membrane vesicles isolated from rabbit cortex showing stimulation of Na^+/H^+ exchange (NHE) and Na^+-HCO_3^- co-transport function (143) and in rat cortical slices stimulation of NHE and Na^+-P_i co-transport (225) by ET-1, which would result in opposite effects on the trans-epithelial. Similar to what we have referred for other paracrine factors that exhibit opposing effects, this has been explained by a concentration-depended biphasic effect of ET-1 in the PT. Regarding PT, it is important to consider the source of ET-1 since the production is scarce in the renal cortex, and thus, ET-1 may not reach a relevant concentration in the vicinity of the PT under physiological conditions. Considering the overall effects of endothelin, the local production of endothelin, and the expression of receptors, it is unlikely that PT contributes significantly to the collected renal tubular effects of ET-1. This is different for TAL, where ET-1 has been demonstrated to inhibit Cl^- reabsorption both in mTAL and cTAL via ET_B (115, 503). Indeed, the local production and release of ET-1 to the basolateral side of IMCD may provide a relevant source for the mTAL ET_B receptor, a process that may contribute to the overall diuretic effect of ET-1.

In terms of interaction with other paracrine factors, it is striking that ET-1 is released in response to stimuli that trigger the release of various paracrine factors in epithelia. Examples are hyperosmotic stress (51, 582), mechanical stimulation (485, 683), and salt loading (8, 291, 387, 508) that are well-documented stimuli for fast ATP release, although ET-1 release apparently is not stimulated by AVP (333, 416). Several data support the notion that ATP works upstream from ET-1 signaling, because inhibition of P2 receptors prevents the flow (485) and NaCl load-induced (207) ET-1 production and release. Remarkably, the endothelinergic system complements the purinergic in terms of signaling kinetics. Where ATP inflicts a fast, shorter-lasting response with rapid clearance of the nucleotide from the extracellular space, a subsequent liberation of endothelin will allow a more sustained transport inhibition over a prolonged period. The combination of the two systems allows subtle cellular signals as flow or NaCl sensing to be amplified and in a paracrine fashion cause a coordinated, sustained tissue response.

It has been speculated that NO in renal epithelia also operates upstream of endothelin, linking mechanical stimulation to endothelin release. Interestingly, this appears not to be the case, since the flow-induced ET-1 release was unaffected by various approaches to inhibit NO generation or signaling pathways (727). On the other hand, ET-1 is able to trigger NO release from IMCD in an ET_B receptor-dependent fashion (275, 637), and it is striking that the CD-specific NOS-1, ET-1 and ET_B deficient mouse strains have a parallel salt-retaining phenotype (193, 272, 574). These data suggest that NO works downstream of ET-1 release, a notion supported in a study of endothelial and CD, specific ET-1 deficient mice (274). In summary, at least for the CD the paracrine factors are nicely ranked from an initial ATP release, over ET-1, to an NO

component that complements each other for a collected tissue response.

Taken together, the endothelin signaling system, in general, inflict tubular transport inhibition, and similar to purinergic signaling is likely to constitute a reno-protective system with the combination of vasoconstriction properties and inhibition of renal tubular transport of NaCl and water. Consistent with this notion, ET-1 signaling has very early been proposed to function as a self-regulatory system to restore tubular integrity after injury (465). Strikingly, this autocrine/paracrine signaling system shows a large gender variation, with male rats lacking the ET-1 induced natriuresis. Following the notion that paracrine signaling provides a certain degree of reno-protection, one could speculate that this will render the male's kidney more susceptible to damage. In this context, it is worth noticing that women repeatedly have been demonstrated a higher prevalence of chronic kidney disease in several meta-analyses (257, 417, 763). However, renal disease progresses faster in men than women, independent of the severity of progression factors such as hypertension, hyperlipidemia, etc. (440, 493, 600), and thus, a gender difference in paracrine protection of the kidney could be relevant.

Bradykinin

Bradykinin is a well-substantiated, vasoactive peptide that, together with Kallidin/kallidin-like peptide, forms the active components of the kallikrein-kinin system. Similar to many of the other paracrine factors, the actions of the kallikrein-kinin system are not confined to a single tissue but have been implicated in as diverse functions as coagulation and pain sensation. In the kidney, bradykinin signaling has been linked to various pathophysiological conditions but actually is a bona fide renal paracrine signaling systems involved in water and salt handling. The vasoactive effect of kinins was initially shown by Abelous and Bardier as marked systemic hypotension after injection of human urine in anesthetized dogs (4). Later the hypotensive substance in the urine was revealed to be an enzyme (kallikrein), which catalyzes the cleavage of kininogen/high molecular weight (HMW) kininogen to bradykinin (Fig. 5) and kallidin in humans or kallidin-like peptide in rats (256). Thus, kinins are parallel to the other signaling peptides cleaved from a pro-peptide, here kininogen predominantly produced by the liver (438, 649). The kallikrein found in urine is predominately active tissue kallikrein released from the tubular cells, which is distinct from circulating plasma kallikrein. In plasma, kallikrein is primarily inactive as pre-kallikrein and prevents overstimulation of the coagulation system (306). Thus, the renal kallikrein is not filtered into the urine (for overview see (79)) but locally produced. Once produced, bradykinin is rapidly degraded via ACE (347) in the endothelial membrane with a half-life of less than 30s in plasma (107). This provides yet another potential role for ACE is expressed in the PT (81) since only 0.2% of bradykinin injected in the renal artery of dogs is found in the urine (436). In addition to the proximal tubule, ACE also shows distinct expression in the CD (81).

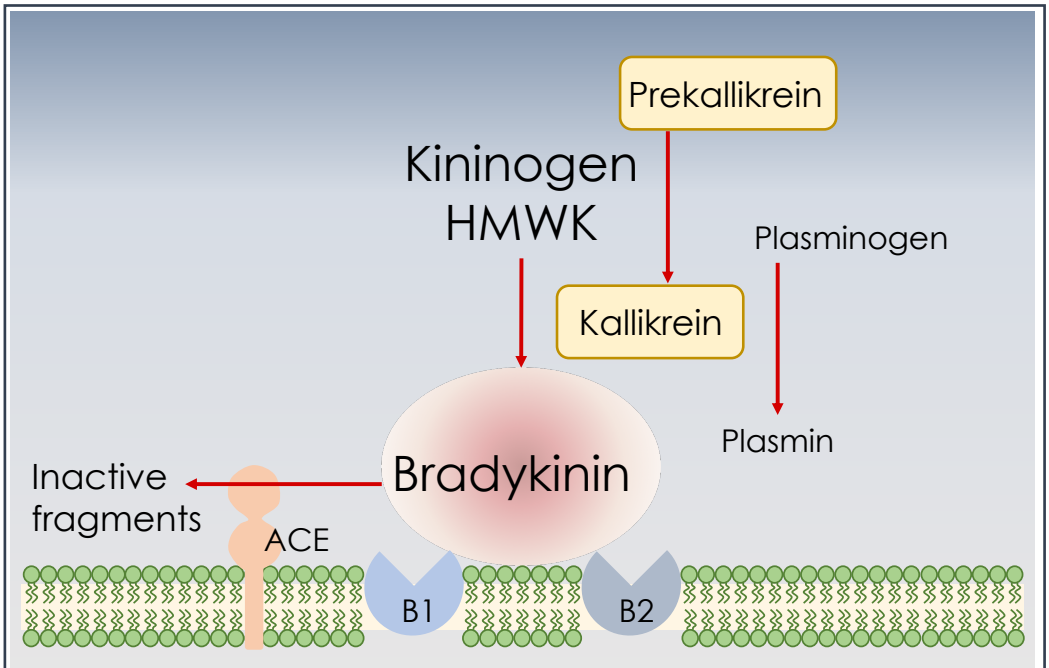

Figure 5 – Arachidonic acid signaling *Overview of the generation pathway for prostaglandins, HETE, and EETs. Abbreviations: COX (cyclooxygenase), EET (epoxyeicosatrienoic acids), HETE (hydroxyeicosatetraenoic acid), HPETE (Hydroperoxyeicosatetraenoic acid), PG (Prostaglandin),*

Bradykinin acts via the G-protein-coupled receptors B_1 and B_2 (for a comprehensive review see (229)). B_2 is generally mediating

the physiological functions of bradykinin and is also the predominant bradykinin receptor in renal epithelia. Initially, the B_2 receptor was via *in situ* hybridization found to localize to PT, thin and thick segments of Henle's loop, DCT, and CD(620) with highest expression in the proximal straight tubule and CCD (397). Immuno-histochemistry confirmed the primary localization in CD, showing most prominent apical but also some basolateral localization (147). These data may suggest that the primary site of action for the kallikrein-kinin system is the CNT and CD. This notion is supported by data showing that kininogen, in addition to the liver, also specifically is produced in the principal cells of the CNT and CD (146, 620) and the finding that kinins are produced in the distal – not in the proximal tubule by the flow stop technique (745).

The renal effects of bradykinin were known long before the signal transduction pathways were established. However, considering the signal transduction pathways in the light of what is known from all the other paracrine signaling systems, it seems evident that bradykinin will add to the long list of paracrine factors that inhibit the transepithelial transport causing diuresis and natriuresis. Bradykinin triggers prompt diuresis and natriuresis after direct injection into the renal artery (31, 250, 732). This finding was combined with an increase in renal plasma flow and, thus, contains a major vascular component. If the vascular component was compensated for, bradykinin still causes a marked diuresis and natriuresis during constant GFR and renal blood flow (610, 611). Considering the localization of the kallikrein-kinin system signaling components, it is likely that the diuretic and natriuretic effect is mainly a collecting duct effect. This notion is confirmed pharmacologically by inhibition of B_2 receptors, and by a following increases Cl^- and water reabsorption in the medullary CD (426). *In vitro* studies showed that bradykinin reduced the oxygen consumption in suspension of rabbit IMCD cells to an extent similar to ouabain and amiloride, which suggests a direct inhibition of Na^+ transport (758). This finding was initially confirmed by direct bradykinin-induced inhibition of Na^+-transport in perfused rat CCD (680) and later by an opposing effect of a B_2 antagonist (613). The most renowned Na^+ resorptive mechanism in CD is the ENaC mediated. Accordingly, a role for ENaC in bradykinin-induced inhibition of CD Na^+ transport was suggested based on cell culture, where bradykinin reduced the amiloride-sensitive transepithelial current (634). These data were later confirmed and refined directly in split open CCD (755), showing concentration-dependently reduced open state probability of ENaC by bradykinin, without affecting the membrane abundance of ENaC (755). It is important to mention that the target for bradykinin-induced reduction Na^+ reabsorption is not fully resolved. Several studies of perfused rat CCD showed that both the transepithelial voltage (572, 679, 680) and the K^+ transport (679, 680) is unaltered by bradykinin, both of which does not support that the bradykinin effect on Na^+ transport is ENaC-dependent. Currently, there are no mechanistic studies that offer other possibilities, although bradykinin has been shown to inhibit the basolateral NHE_1 in IMCD cell lines (427). However, this transporter does not support transepithelial Na^+ reabsorption. Concerning anions, bradykinin has been demonstrated to reduce AVP-induced Cl^- absorption in parallel to the reduction in Na^+ reabsorption, whereas it does not affect the HCO_3^- transport in rat CCD (679). In summary, the overall effect of bradykinin on the CD transport is an apparent inhibition of both Na^+ and Cl^- transport. In this context, it is worth noticing that mice lacking the B_2 receptor and exposed to high NaCl load during embryogenesis show a marked renal phenotype with tubular dysgenesis of the distal tubule, and cyst formation (148). These data suggest that an inability of bradykinin-dependent reduction of the distal tubular Na^+ transport renders the CD susceptible during NaCl load and is in line with the notion that paracrine signaling provides tissue protection.

Regarding the water transport, the previously mentioned studies from Tomita et al. showed that the fluid flux was unaltered under basic conditions but markedly reduced by bradykinin during AVP-stimulated transport (679, 680). This effect was later confirmed to be caused by an interference of bradykinin with the apical translocation of AQP2 in CD8 cells (654) apparently without affecting the cAMP levels (393). The effect of bradykinin on water transport may easily be much more pronounced *in vivo* than in isolated tubules because bradykinin also has been shown to increase the medullary blood flow (406). This will, in turn, increase the washout of the renal medulla and thereby support the diuretic effect.

So what triggers bradykinin signaling? It has been demonstrated that a low NaCl containing diet markedly increased kallikrein excretion into human urine (for review see (454) and that this match with an increase of interstitial bradykinin both

in cortex and medulla of anesthetized dogs (610, 611). This immediately fits data showing that a high salt diet reduces renal kallikrein and B_2 receptor expression in the kidney (145). Collectively this would result in increased bradykinin-dependent diuresis and natriuresis in a situation with reduced Na^+ in the diet. This response may potentially explain why low NaCl intake reduces the circulatory volume and lowers systemic blood pressure. However, in terms of body salt homeostasis, it makes little sense that reduced NaCl availability increases the Na^+ wasting by the kidney, and thus, the system has the potential to cause Na^+ depletion. Therefore, the bradykinin system must be viewed in the context of the actions of other local and systemic regulators.

On that note, bradykinin has been shown to interact with several of the other paracrine signaling pathways. Activation of the B_2 receptor has been demonstrated to increase NO production both in the vasculature (235) and in renal epithelial cells (353). Thus, NO seemingly works downstream of bradykinin, similar to what is observed for the endothelin and purinergic system. The effect of bradykinin is closely associated with that of prostaglandins. In early studies, there was not an apparent discrepancy between the direct vascular effects of bradykinins and those mediated by bradykinin-induced release of prostaglandins (410, 659). Thus, prostaglandins work downstream from the kallikrein-kinin system and support and modulate its effect. More details on the interaction are provided below after the presentation of the renal prostaglandin system.

Recent data propose an interaction between the bradykinin and collecting duct renin signaling. They showed that in M-1 cells bradykinin increase the abundance of pro-renin/ renin mRNA and the renin release to the supernatant. This fits nicely to the low immunoreactivity of pro-renin in the collecting duct of B_2 deficient mice (353). These findings are potentially interesting because the pro-renin/renin and the kallikrein-kinin system have opposing effects on tubular transport. If substantiated, this study could imply that there is a feedback inhibition on the kallikrein-kinin system, which potentially could avoid complete Na^+ wasting in response to a low NaCl intake. Overall, the kallikrein-kinin system clearly supports the notion that paracrine signaling is reno-protective, although the effect of bradykinin primarily affects the epithelium without having dramatic effects on the renal vasculature (140).

3.4 Renal tubular system and reactive oxygen species

As mentioned above, other reactive oxygen species than NO have been established as physiologically relevant for the overall renal function. Reactive oxygen species are local mediators by nature and shown to have significant impact on the conductivity of the renal vasculature. These gaseous signaling molecules are present in the microenvironment in the kidney (89), and thus, it is relevant to address, whether they have a place in the regulation of tubular transport.

Unfortunately, there is very little evidence for a physiologically relevant effect of either O_2^- or H_2O_2 in the PT. Apparently, the PT expresses NOX_4 in relevant amounts (198), and thus, the basis for local generation of O_2^- should be in place. There is evidence for O_2^- (607) and H_2O_2 (606) affecting apical Cl^-/HCO_3^- transporters in cells derived from PT. Since this transporter has limited implication for the overall transepithelial transport of NaCl it is hard to extrapolate the findings into the context of directional transport. It has to be emphasized that even though a solid effect established in cell culture were to indicate a direction of the overall effect on transepithelial transport, it is essential to carry out direct transport studies on isolated perfused tubules to determine the collective effect of a given perturbation on tubular transport. However, there is only one study that directly measures transepithelial transport in isolated, perfused rat PT (486). The study indicates that inhibition of NOX in this segment has minuscule effect under physiological conditions (486). This notion is indirectly supported by *in vivo* data showing that O_2^- under physiological conditions has little to no importance for the PT transport, whereas during diabetes mellitus, an overactive NOX activity increases O_2^- production, which sequentially stimulates PT Na^+ reabsorption (495).

The scenario is quite different in the thick ascending limb. Here O_2^- clearly stimulates the transepithelial NaCl transport (472) both via direct stimulation of NKCC2 (299) and indirectly by modifying the NO availability (470). Newer data support that an acute increase in tubular flow increases NOX4 activity and thereby increase transepithelial transport in TAL via an acute stimulation of NKCC2 (557). This O_2^- induced stimulation of NKCC2 has been suggested to be mediated via PKC (604), which contrast the discussion of the effect of Ca^{2+} and PKC activation earlier in this review (under section3.1; *P2*

Receptors in nephron and collecting duct; effect on transport).

In the collecting duct, again, a substantial amount of the information comes from cell culture models. In A6 cells, both O_2^- and H_2O_2 have been suggested to increase the ENaC activity (398, 399, 752). The evidence for that this also is the case in the intact tubule is scarce. However, data support that the AngII-mediated increase ENaC activity in CD is mediated via NOX activation and O_2^- generation (644). Interestingly, O_2^- has only a modest impact on basal transport of urea in isolated perfused IMCD (773). However, when the O_2^- production is increased, it causes a very acute stimulation of the urea transport in this segment (773), supporting the overall notion that O_2^- stimulated transport in the CD.

In conclusion, the reactive oxygen species remark themselves by virtually being the only autocrine/ paracrine signaling molecule that stimulates tubular transport rather than inhibiting it. In that sense, O_2^- opposes the renoprotection provided by the larger part of the other mentioned paracrine factors (Table 2). Therefore it is interesting that lack of NOX4 function renders the PT more susceptible to acute cell death during renal ischemia and reperfusion (445), to contrast agent-induced acute renal damage (295) and that H_2O_2 has been shown to elongate primary cilia in renal tubules in the remaining kidney after unilateral nephrectomy (231). These studies support the notion that O_2^-/H_2O_2 promote renal epithelial cell differentiation and inhibition of various types of cell death, which matches a simultaneous stimulation of the epithelial transport to sustain a normal renal function.

Upfront, this could seem contradictory that paracrine factors oppose each other. However, one has to bear in mind that the reactive oxygen species are produced in situations where oxygen is plentiful and not used by the tissue in the rate that it is provided. Taken the ischemic reperfusion situation as an example, there would be a need to shut down transport in the ischemic phase and reassume normal function as adequate O_2 levels return to the tissue. It is therefore interesting that ATP has been demonstrated to be released in the early phases of ischemia as, for example, in the brain (300), whereas O_2^- and H_2O_2 is primarily generated as the O_2 returns to the tissue (for review see (240). Thus, these paracrine factors are not supposed to work under the same condition but serve a completely different function in the maintenance of renal structure and function.

3.5 Prostaglandins in transport regulation

Prostaglandins are universal signaling molecules that can act both as hormones and in local signaling. Prostaglandins have a marked effect in the vasculature and are important for the sensitivity of the TGF response. Prostaglandins are filtered, and thus, have the opportunity to act on renal epithelial cells both from the apical and basolateral side. Interestingly, an early study of tubular handling of PGE_2 shows that only around 60% of the PGE_2 injected in the early PT is recovered in the urine. This means that a large part of tubular PGE_2 is either bound or metabolized during the passage of the tubular system, primarily in the loop of Henle (311). Inhibition of prostaglandin synthesis markedly increased the Na^+ and Cl^- concentration in the interstitium of the renal medulla (182), indicating that prostaglandins are essential regulators of the urinary concentrating mechanism and presumably inhibit TAL function.

As discussed earlier for other signaling molecules, the filtered plasma-prostaglandins that appear in the pre-urine are not to be considered a local signaling molecule and thus, are not further considered. Meanwhile, the arachidonic acid pathway is demonstrated to be functionally active in many types of renal epithelial cells providing a local source of arachidonic acid derivatives. In 1979 James M. Irish III convincingly showed that PGE_2 is secreted along the entire PT length (285). However, it was later established in micro-dissected tubules that the CD is the main site of PGE_2 production, with some contribution from thin descending limb and TAL (52). To support the notion of local tubular prostaglandin production, the relevant enzymes of the arachidonic pathway have to be expressed in the renal epithelial cells (Fig. 3). The non-inducible form of the cyclooxygenases, COX_1, has not been investigated extensively in the kidney. It has been shown to be expressed in both cortex and medulla in the developing rodent kidney but is mostly confined to the medulla in the adult kidney as established by RT-PCR, with an apparent upregulation on a high salt diet (44). Interestingly, specific COX_1 inhibition reduces the total prostaglandin levels both in the cortex and the medulla (521), and thus, COX_1 may potentially support prostaglandin production in all the renal tubules. In contrast, there has been a quite marked interest in COX_2 expression and function under physiological and pathophysiological conditions. Under baseline conditions, animals do show a low degree of COX_2 expression in most tissues. As previously mentioned, a normal kidney

almost exclusively expresses COX_2 in the macula densa, with some expression in the CD and medullary interstitial cells (223) (448). However, under pathophysiological conditions like ureteral obstruction or acute renal injury, COX_2 expression is generally upregulated and extends to other parts of the tubular system and interstitial cells allowing a more widespread influence of prostaglandins on renal function (for review see (448)).

Effects of prostaglandins on epithelial transport in the kidney

PGE_2 has been shown to be the most abundant prostanoid in the mouse kidney, followed by PGI_2, $PGF_{2\alpha}$, and thromboxane A_2 (521). Early it was clear that PGE_2 had a significant impact on tubular transport. It was unambiguously demonstrated in anesthetized dogs that injection of PGE_2 directly into the renal artery increased natriuresis without any general hemodynamic effect or changes in the non-injected kidney (248). These data suggest that PGE_2 inhibits epithelial transport. The mechanism of transport inhibition has, however, been debated. Initially, PGE_2 in high concentrations ($<10^7$ mM) was found to accelerate cAMP production in dissected rabbit TAL (434) and CCD (623). Interestingly, the same study demonstrated that lower concentrations of several prostaglandins, including PGE_2, markedly reduced the AVP-induced cAMP generation, which immediately suggests more PGE_2 receptor subtypes. Moreover, PGE_2 trigger an increase in $[Ca^{2+}]_i$ in isolated CCD (245) and blocking this completely abolished PGE_2-induced reduction of the transepithelial potential (246). According to these findings, PGE_2 has later been established to be the prime agonist for four types of receptors; E-prostaglandin receptor 1-4 (EP_{1-4}). All these receptor subtypes are expressed in the kidney. EP_1 is confined to the CD as shown by *in situ* hybridization as well as functionally by an increase $[Ca^{2+}]_i$ and inhibition of the Na^+ reabsorption in perfused rabbit tubules (224). EP_2 is primarily expressed in descending thin limb and vasa recta, as shown by RT-PCR on dissected tubules and vasculature (293). The expression of EP_2 in rats was also addressed functionally in micro-dissected tubules that showed a clear increase in cAMP upon stimulation of the descending thin limb by the EP_2 receptor agonist butaprost, whereas this was not the case in CD, which lacked EP_2 PCR product (293). The EP_3 receptor shows a broader distribution based on *in situ* hybridization and RT-PCR of dissected tubules; cTAL/mTAL, CNT, CCD/IMCD and possibly also CNT (59, 656), whereas the EP_4 receptor, in terms of tubular expression in rats, is confined to DCT and CCD (293). Thus, the action of locally released PGE_2 depends both on the absolute concentration in the tissue and the expression pattern of specific receptors.

In the proximal tubule, PGE_2 stimulates PO_4^{3-} transport and counteracts the inhibitory effect parathyroid hormone (PTH) on PO_4^{3-} uptake (127). In support of this, the adenylyl cyclase activity is markedly reduced upon exposure to PGE_2 (128), which is immediately consistent with stimulation of an EP_3 receptor that couples to $G_{\alpha i}$ (361). Because of the apparent minor PGE_2 release by the PT, these effects may qualify as paracrine signals but rather reflect a systemic effect of prostaglandins. Nevertheless, PGE_2's effect on PT is not immediately in line with an overall inhibitory effect on epithelial transport by prostaglandins in the other segments. There are, however, later reports that do not fit the reported EP_3-mediated reduction of cAMP production in PT. In a series of papers using opossum kidney cells as a model for PT, it was suggested that PGE_2 functions as an autocrine/paracrine mediator of epithelial growth factor (EGF)-induced stimulation of organic anion transporter OAT1 (568, 569). It was later confirmed that both EGF and PGE_2 stimulated basolateral organic anion transport measured as H^3-PAH uptake in perfused rabbit PT (566). Based on cell culture data, the PGE_2-mediated effects were shown to require activation of adenylyl cyclase and an increase in cAMP and PKA activation. The effect was inhibited by butaprost, which implicates that the effect required EP_2 receptor activation (569). Interestingly, PGE_2 is in itself a substrate for OAT_1 and OAT_3. In cell culture (NRK-52E cells) long-term exposure resulted in down-regulation and reduced expression of $OAT_{1/3}$ (567), which counteracts the initial, acute effect of PGE_2 on organic anion transport. The notion that prostaglandins stimulate PT secretion via an increase of cAMP is supported by a study showing that PGE_1 and PGE_2 stimulate both transcription and activity of the Na^+/K^+-ATPase in PT cells (252). Some studies actually suggest that PGE_2 reduces the driving force for transepithelial reabsorption in proximal tubule. A study of the Na^+/K^+-pump activity in isolated pig PT basolateral membrane shows the Na^+/K^+-pump activity to be inhibited via

a reduction in cAMP and PKA activity (96, 374) therefore opposing all of the abovementioned studies in terms of transport direction and partially also regarding the signal transduction. In summary, the overall picture for the proximal tubule is that the prostaglandin PGE_2 stimulates PT transport function, both the reabsorption of various ions and the specific secretion of xenobiotics and PGE_2 itself. Therefore, the PT is not responsible for the overall prostaglandin-induced diuresis and natriuresis. Moreover, PGE_2 should not show a protective effect for proximal tubular cells. In support of this, PGE_2 formation has been suggested to mediate cisplatin-induced PT-injury (162), contribute to ischemia-reperfusion (570), and albumin-induced PT injury (770).

The TAL has a relatively low cyclooxygenase activity compared to other segments but is readily able to oxygenate arachidonic acids via the P_{450} systems supporting HETE and eicosatetraenoic acids EET production (163). However, COX-dependent PGE_2 and $PGF_{\alpha 2}$ can be released in low amounts from TAL (163), emphasizing that prostaglandins can support paracrine signaling in TAL despite a modest COX activity. In TAL, it has been reported that PGE_2 dampens the stimulatory effect of AVP on transepithelial transport by preventing the activation of adenylyl cyclase (105). In agreement with this, PGE_2 has been demonstrated to markedly reduce the Cl^- reabsorption (104, 631) in TAL via NKCC2 (303). This is supported by a study that reports increased expression of NKCC2, specifically in response to COX-inhibition (161). Moreover, the inhibitory effect on the transepithelial transport by PGE_2 may be further supported via reduction of the basolateral Na^+/K^+-pump activity by PGE_2 (552), although the effect on the Na^+/K^+-pump activity has been suggested to mainly be secondary to inhibition of NKCC2 (303). Although Na^+/H^+ exchange does not contribute significantly to the overall Na^+ reabsorption of TAL, PGE_2 has been shown to inhibit the NHE_3 activity and HCO_3^- absorption in rat mTAL fitting with the notion of transport-inhibition by prostaglandins in TAL (54, 209). This effect is presumably mediated by EP_3 since this receptor couples to G_i. Apparently, PGE_2 does not influence transport in non-activated tubules, which fits with $G_{\alpha i}$ coupling that requires significant concentrations of cAMP to exhibit its function (105). Regardless of the signal transduction pathway, these results immediately match the previously mentioned reduction of the Na^+ and Cl^- concentration in the interstitium of the renal medulla in response to prostaglandins (182). Interestingly, AVP has been suggested to dampen the local effect of prostaglandins by reducing the availability of arachidonic acid by decreasing the expression of group VIA phospholipase A_2 (479). These data univocally suggest that PGE_2 markedly reduces transport function in TAL and that this effect may be the primary mechanism by which prostaglandins evoke the overall diuretic effect.

The collecting duct is particularly interesting with regard to paracrine prostaglandins because it is the prime production site for renal prostaglandins. Thus, it is not surprising that the PGE_2-induced natriuresis, in addition to TAL, also is supported by PGE_2-induced transport inhibition in CD. Because PGE_2 inhibits the TAL function, the overall water reabsorption in CD will also be diminished as a result of the reduced osmotic gradient. The effect of PGE_2 on water-permeability of the CD is not straightforward. PGE_2 has been shown to decrease water permeability in isolated perfused CCD when these were pretreated with AVP (247). This is consistent with the overall renal effects of PGE_2, supporting the reduction of TAL transport in producing the diuretic effects of PGE_2. Contradictory to this, the same study demonstrates that PGE_2 in the absence of AVP increases the water permeability of CD (247). This discrepancy is believed to reflect differentiated action through various prostaglandin receptors. Thus, the inhibitory effect of PGE_2 was suggested to be mediated via G_i-coupled EP_3, whereas the increased water permeability in the absence of AVP via the EP_2 (247). Based on this, activation of EP_2 has been pursued as a potential way to circumvent the lack of V_2 receptors in certain types of nephrogenic diabetes insipidus. Despite the previous observation that the EP_2 receptor was not present in CD neither on mRNA level or functionally (293), it has been demonstrated that prostanoid-receptor 2 agonists concentration-dependently increase the trafficking of AQP2 to the apical membrane of MDCK cells and rat CD (462). Moreover, the prostanoid-receptor 2 agonist also reduced the urine output in rats treated with a V_2 receptor antagonist (462). Collectively these data support that the effects of PGE_2 in CD will promote the overall prostaglandin-mediated diuresis. However, in the absence of AVP or V_2 receptor actions, PGE_2 can support an increased water permeability in the CD. Regarding ion transport in the CD, PGE_2 has been shown to reduce

the transepithelial potential, and thus, inhibit Na^+ reabsorption in rabbit CD (247, 632) most likely via EP_1 receptor (208, 247). This effect is mirrored when studying Cl^- transport with or without blockers of prostaglandin synthesis. Both in the TAL but also in CCD and OMCD inhibition of prostaglandin synthesis increase Cl^- absorption confirming the inhibitory effect of PGE_2 in the CD (255).

Integrating the effect of all the segments, PGE_2 does as the main renal prostaglandin cause diuresis and natriuresis. This effect is mainly mediated via a reduction of TAL function resulting in reduced medullary accumulation of osmolytes, and thus, reduced driving force for water reabsorption. This effect is supported by a reduced water permeability in the collecting duct because this effect is exclusively seen in the presence of AVP. The natriuresis also results from a combined effect of reduced Na^+ absorption in TAL and reduced ENaC-mediated Na^+ absorption in CD. Thus, the renal prostaglandins support the overall notion of paracrine signaling being reno-protective even though the inhibitory effect on tubular transport is not mirrored in a clear directional vascular effect. The exception is the proximal tubule, where PGE_2 stimulates tubular transport and accordingly is associated with renal tubular injury.

Cross talk between prostaglandin other paracrine factors

As previously mentioned, purinergic signaling is likely to be upstream in the local signaling cascades. The first step in the prostaglandin synthesis is catalyzed by phospholipase A2, of which some of the plasma membrane-associated variants are activated by Ca^{2+} in the micromolar range (442). Thus, it is likely that P2 receptor activation, in general, will result in activation of the arachidonic pathway. In support of this notion, Welch et al. demonstrated that concentration-dependent stimulation of P2 receptors by ATPγS caused a COX_1-dependent release of PGE_2 in isolated IMCD (721).

Similarly, arachidonic acid derivatives have been speculated to be a significant player in renin release by the JG cells. Renin release from JG cells requires an increase in cAMP and PKA activation (173) and is further supported by cAMP-induced increase in the renin production via cAMP response element-binding proteins (CREB) (324). Thus, one would expect that PGE_2 in JG cells would increase both acute and chronic renin release. Since PGE_2 production in the renal tubules occurs mainly in CD, it has been studied whether activation of PGE_2 receptors is involved renin secretion in this segment. This sentiment has so far only been demonstrated in cultured M1 cells, where PGE_2 was shown to increase both the intracellular levels of cAMP and renin mRNA and protein levels (562).

In the vasculature, there are significant interactions between prostaglandins and endothelin. Therefore, it was reasonable to assume that the same would be the case in the renal tubular system, particularly when considering the synergistic effects of these two paracrine molecules. Early studies showed that that prostaglandins were likely to work downstream of endothelin, as both ET-1 and ET-3 receptor stimulation resulted in PGE_2 formation in isolated rat IMCD (334). Therefore, it was surprising that ET-1 deficient mice showed an increased urinary PGE_2 excretion that was intensified during increased NaCl diet (195). This effect was not caused by upregulation of either COX_1 or COX_2 in the collecting duct, and thus, it was concluded that endothelins are not the primary regulator of PGE_2 release in the collecting duct. Similar to endothelin bradykinin has been suggested to mediate prostaglandin release in the collecting duct in CD cells isolated from rabbit (350) via PKC and MAPK-depended stimulation of phospholipase A_2 (351). These findings have, however, not been evaluated *in vivo*, and thus, it is not known whether this similar to the ET-1 signaling may not be relevant in a physiological setting.

Other arachidonic acid derivatives

As mentioned, not all tubular systems show extensive COX-expression, and, at least in the TAL, P_{450} is responsible for generation of the major fraction of arachidonic acid derivatives (163). Central P_{450} enzymes are also expressed in other parts of the renal tubules. CYP2J5 is expressed extensively in the kidney primarily in the PT and CD (389), whereas CYP4F2 and CYP4A11 are exclusively expressed in S1-S2 segments of PT (355). The main function of the P_{450} system in terms of arachidonic acid derivatives is to produce various variants of HETE and EET (Fig. 3). With a local production site in the renal tubules (163), it is reasonable to assume that they function as paracrine effectors of the tubular function. Studies of the effects of HETE and ETT on the renal function suggest that these paracrine substances, similarly to the prostaglandins, induce diuresis and natriuresis (130). This notion is circumstantially supported by a

study indicating that specific inhibition of 20-HETE production in the renal medullar of rats causes substantial systemic hypertension (629).

In the proximal tubule, products of P_{450}-dependent metabolism of arachidonic acid have been demonstrated to markedly affect tubular transport. The metabolite that is mainly produced in PT is 20-HETE, which, together with 12-HETE, was shown to reduce the Na^+-depended PO_4^{3-}uptake (172, 605). Based on these data, 20-HETE was suggested to mediate the PTH effects on PT PO_4^{3-} uptake (605). In support of an inhibitory effect of 20-HETE on PT transport, 20-HETE was shown to markedly reduce the PT Na^+/K^+-pump activity (450, 464, 536) via activation of PKC (450). This reduction of ion transport directly influences the volume-transport in the PT. Thus, inhibition of the 20-HETE production in the proximal tubule was shown to increase volume reabsorption in perfused tubules (536). In summary, 20-HETE produce significantly transport inhibition in PT supporting the diuresis and natriuresis generally produced by P_{450}-dependent arachidonic acid derivatives.

In the thick ascending limb, the most prominent P_{450} metabolites are 19-HETE, 20-HETE, and 20-COOH-AA (80). Interestingly, the effect of 20-HETE is similar to that in the PT. Both arachidonic acid and 20-HETE markedly inhibit NKCC2 (152, 153), where the effect of arachidonic acid required cytochrome P_{450} activity (153). In addition to the effect on NKCC2, the ROMK channel in rat TAL was inhibited by either arachidonic acid or 20-HETE, where the arachidonic acid effect was abolished by inhibition of P_{450} but not by COX-inhibition (711). This not only supports that 20-HETE inhibits transport in TAL but also strengthens an active role of P_{450} in the segment. Interestingly, an increased 20-HETE release from TAL on a low K^+ diet has been suggested to explain the reduced urinary concentration ability during hypokalemia (222). It must be mentioned, however, that one study does not support the data discussed above. Ito and Rohan only found an inhibitory effect of 20-HETE on the Cl^--uptake or the transepithelial voltage change just in mTAL of salt-sensitive Dahl rats but not in the healthy controls (287). This discrepancy cannot be attributed to differences in the used concentrations of 20-HETE.

In the collecting duct, the open state probability of ENaC has been demonstrated to be markedly reduced by 11,12-EET in cultured M1 cells (708). This finding was confirmed in CHO cells and expanded to include 8,9-EET, and 14,15-EET, whereas the main HETE-subtypes produced in the collecting duct (5, 12, 15-HETE) did not affect channel open state probability (489). The study shows that EET's can function as local modifies of ENaC function and that the EET effects were mimicked by overexpression of CYP2C8 and eventually that ENaC activity was increased by general P_{450} inhibition (489).

In summary, these data suggest that P_{450} metabolites are paracrine signaling molecules that promote diuresis and natriuresis as a result of epithelial transport inhibition. Interestingly, 20-HETE is remarkable in the sense that a substantial part of its diuretic/natriuretic effects includes functional inhibition of PT function. There is very little handle on how the P_{450} metabolites interact with other paracrine factors, although 20-HETE has been shown to have a synergistic effect with dopamine regarding Na^+/K^+-pump inhibition in PT (313). However, 20-HETE is another example of a paracrine factor that is likely to mediate a robust reno-protective effect through its combined inhibition of tubular transport and vasoconstrictive properties.

3.6 Intratubular dopaminergic signaling

Dopamine and its receptors have been identified as a relevant natriuretic system in the kidney that is functional during states of positive Na^+ balance. Similar to many of the aforementioned paracrine factors, dopamine has been demonstrated to have a clear vascular effect, which in the case of dopamine, is primarily neurogenic. Systemic application of dopamine causes vasodilation (262) and thus, increase GFR (262). However, the powerful natriuretic effect of externally added dopamine could not be explained by the impact on GFR alone (262), implying a tubular effect, which was shown to result from inhibition of reabsorption in both the proximal and distal tubules (269). Importantly, the intrarenal dopaminergic signaling is now fully established as a paracrine signaling system, with all the relevant components expressed in the various renal tubules. The precursor L-DOPA is freely filtered into the pre-urine and taken up by the proximal tubule cell via Na^+-coupled transport (618) mediated by L-type amino acid transporter 2 (LAT2)/ SLC7A8 (76, 737). L-DOPA is processed by the PT aromatic L-amino acid decarboxylase (AACD), known as DOPA decarboxylase (DDC),

transported into acidic vesicles via vesicular monoamine transporter 1 (VMAT1) (408) and primarily released to the lumen. Since AACD is mainly expressed in the PT (6, 46, 242), this segment is the prime site of dopamine release in the renal tubules. During excess Na^+ loading conditions, dopamine can be found in increased amounts in the urine (457), a feature, which is reduced in several forms of hypertensive patients (203). It continues to be unresolved what causes the dopamine system to become activated in states of high Na^+ uptake, although it has been shown that AACD is upregulated during high NaCl diet (243, 587). Some physiological sensory mechanisms must be called upon to permit in a feedback-controlled manner to then act as an intrarenal Na^+ sensor that activates this system.

Dopamine inflicts its effect via five specific dopaminergic receptors grouped as D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4), which activate G-proteins either as homomers or heteromers (for review see (37)). The dopaminergic receptors are expressed in most tubular segments. The D_1 receptor is the primary receptor mediating the dopamine-dependent natriuresis and has been shown to be expressed in PT and CD (11, 451, 452) both on the apical and basolateral side. The D_3 receptor apparently is found in the PT, DCT, and CD (453), whereas the D_4 receptor is exclusively found in CD (643). In these segments, dopamine has been demonstrated to acutely inhibit the basolateral Na^+/K^+ ATPase (28, 84, 175, 588, 652), which would lead to a marked reduction of Na^+ reabsorption in the kidney.

In the proximal tubule, dopamine, in addition to the effect on the Na^+/K^+-ATPase, has also been demonstrated to inhibit apical NHE_3 both directly (156, 157, 292) and by reducing the activity of the ubiquitin-specific peptidase 48 and thus, increase degradation of NHE_3 (17). Paracrine dopamine effects have also been shown to inhibit Na^+-PO_4^{3-} absorption in PT, leading to increased urinary P_i excretion (27, 117, 494). In the TAL, the inhibitory effect of dopamine on the Na^+/K^+-ATPase is paralleled by a marked inhibition of NKCC2 (214, 215, 714).

The renal dopaminergic signaling system seemingly stands alone with very few reports on interaction with other paracrine factors. One exception is the arachidonic acid derivatives, where some sparse indications of intertangled effects with dopaminergic signaling exist. Dopamine has been shown to trigger PGE_2 release from IMCD cells (271), and dopamine has been shown to prevent the increase in COX_2 expression observed in response to a high NaCl-diet in rodents (760). The only indication of functional interaction between these two systems comes from studies that suggest that 20-HETE mediates the inhibitory effect of dopamine on NKCC2 (215, 270). Despite that the dopaminergic system is unique in renal paracrine signaling, it obeys to the overall notion that paracrine factors inhibit tubular transport and inflict diuresis and natriuresis.

According to the suggestion that transport inhibition is reno-protective, mice lacking catechol-O-methyl-transferase (COMT) for dopamine degradation specifically in PT and thus have higher intrarenal dopamine concentration are protected against renal injury induced by AngII (747) or diabetes mellitus (762). The opposite is the case if the dopamine production is reduced, as is the case in mice with PT-specific deletion of aromatic l-amino acid decarboxylase (AACD), which converts L-DOPA into dopamine. These mice have markedly increased blood pressure, reduced stimulated natriuresis, increased renal infiltration of leukocytes, lymphocytes and macrophages, and a shorter life span (761). The picture is not quite as clear in humans. Here individuals with SNP variations in AACD with reduced enzyme function (Vmax and Km) apparently have a higher dopamine concentration in the urine (418). People carrying an AACD with reduced function actually secrete more dopamine to the urine and also present with higher urinary Na^+ excretion (418), which fits the notion that dopamine inhibits tubular Na^+ reabsorption.

3.7 Intratubular signaling with α-ketoglutarate

The intrarenal dopaminergic system is one example of how a substance released from one tubular segment can cause specific signaling in downstream segments by following the flow of the pre-urine. This principle is likely to be true for many of the other paracrine signaling systems that express apical receptors, like the purinergic system. However, the principle is more easily documented when a signaling factor is exclusively released upstream and exclusively signals downstream. Therefore, this principle appears elegantly demonstrated by the intratubular α-ketoglutarate signaling.

α-ketoglutarate (α-KG) is known as an important intermediate substrate in the citric acid

cycle. For renal physiologists, it is an essential substrate that allows the tertiary active transport of para-amino hippuric acid from the blood to the PT lumen via the basolateral organic anion transporters OAT_1 and OAT_3 (335, 520, 592, 646). Interestingly, in PT α-KG is in addition to the Krebs cycle, also formed by during ammoniagenesis (for review see (581)). Recently, α-KG has been proposed as a novel signaling molecular for intraluminal signaling from the early- to the distal part of the renal tubular system (Fig. 6). One of the characteristics that set α-KG aside from other paracrine signaling molecules is that it requires substantially higher concentrations (mM) of ligand to stimulate the oxoglutarate receptor 1 (OXGR1 or GPR99)(244). The EC_{50} for α-KG at the OXGR1 is around 70 µM, and full stimulation is first seen at 300 µM (244). This EC_{50} does, however, fit the relatively high concentration of α-KG in the urine, ranging from 0.2-0.8 mM (217, 593). The corresponding human plasma concentration of α-KG has been measured to be 8.5-12 µM (227, 542, 699), which essentially means that α-KG is either up-concentrated along the tubular system or secreted into the renal tubule (Fig. 6). Considering the up-concentration, the freely filtered α-KG (95) would reach a concentration of around 1.5 mM in the CD lumen, if α-KG was not handled by the renal tubular system. Under normal conditions with slightly acidic urine, practically all of the filtered α-KG is absorbed in PT (599, 696). However, during alkalosis, the urinary excretion of α-KG is markedly increased (164, 403), and micro-puncture data suggests that PT handling of α-KG during alkalosis changes from reabsorption to secretion (164, 403). It has been suggested that increased urinary output of α-KG might result from increased ammoniagenesis (218). However, this is not likely to be the case in the alkalosis-induced urinary α-KG excretion, since the ammonium production in this situation is minimal. Whether or not the α-KG is secreted by the PT or the filtered α-KG is not absorbed, alkalosis markedly increases α-KG concentration in the urine as a result of an altered proximal tubular function, which potentially allows OXGR1 activation at distal sites.

In the original paper, introducing α-KG as a paracrine factor for regulation of renal tubular transport, Tokonami et al. demonstrated that luminal content of α-KG causes a Cl^--dependent HCO_3^- secretion via OXGR1 expressed in the β-intercalated and the Non-α/Non-β-intercalated cells of CNT and CD (674). Interestingly, the urinary HCO_3^- secretion was markedly blunted in OXGR1 receptor-deficient mice, which also showed a marginally lower urinary pH and higher excretion of titratable acid (674). The notion that α-KG is a paracrine signaling molecule in the kidney was supported by a later study showing that the pendrin-dependent Cl^- reabsorption similarly is stimulated by α-KG via OXGR1 (Fig. 6)(358). This study further suggests that the α-KG-dependent activation of HCO_3^- secretion and Cl^- reabsorption required PKC activation and, thus, a G_q-protein-coupled process (358). Both studies support that an increased baseload or acid loss

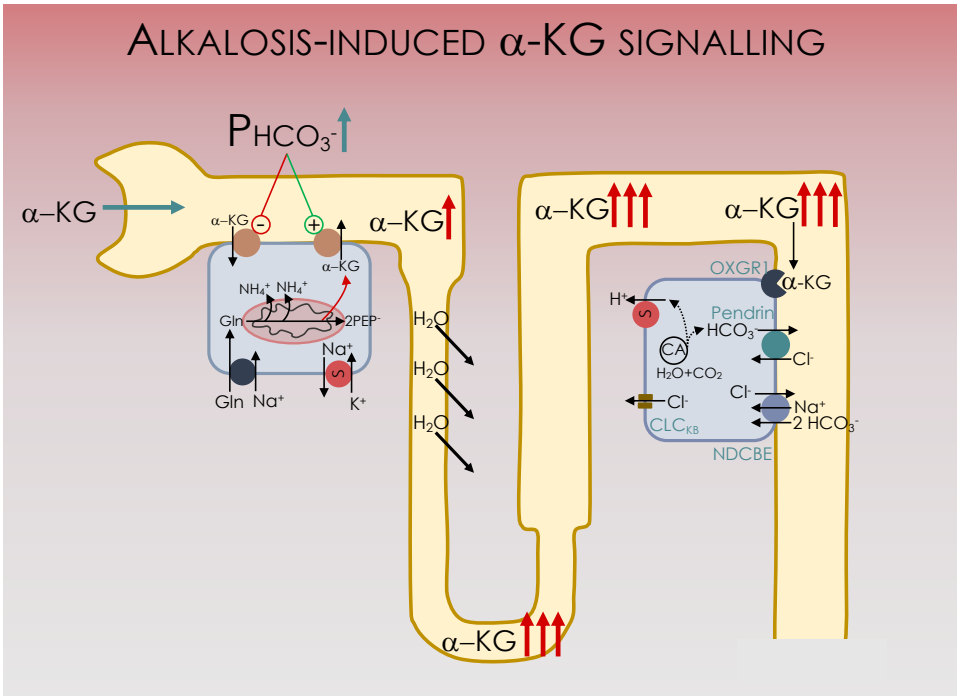

Figure 6 - Intratubular signaling with α-ketoglutarate Schematic of the intrarenal α-ketoglutarate signaling during systemic metabolic alkalosis. The alkalosis inhibits the α-KG reabsorption in PT, which, together with a possible stimulation of tubular secretion, increase the intraluminal α-KG. The α-KG is further increased as water is reabsorbed along the renal tubules and reaches the CD at high concentration. Here it stimulates the HCO_3^- secretion or the NaCl reabsorption.
Abbreviations: α-KG (α-ketoglutarate), CA (carbonic anhydrase), ClC_{KB} (chloride channel KB), Gln (glutamin), NDCBE (Na^+-driven Cl^-/HCO_3^- exchanger), OXGR1 (2-Oxoglutarate receptor 1), PEP^- (phosphoenyl pyrovate), $PHCO_3^-$ (Plasma concentration of HCO_3^-).

resulting in metabolic alkalosis triggers an immediate increase of base secretion by the kidneys mediated by α-KG-dependent intraluminal signaling.

In addition to keeping the acid/base homeostasis, α-KG has been suggested to participate in renal Na^+ handling. In the CD, Na^+ is primarily reabsorbed in the principal cells through the renowned electrogenic ENaC mediated pathway. However, part of the Na^+ arriving in the CNT and CD has been proposed to be reabsorbed in an electroneutral, thiazide-sensitive fashion as transcellular transport in the pendrin positive intercalated cells (Fig. 6)(365). This electroneutral NaCl reabsorption requires several previously mentioned components, including pendrin that provides the luminal Cl^- for the Cl^--dependent HCO_3^- secretion in CNT and CD (314, 551, 627). To support NaCl reabsorption, pendrin is suggested to functionally couple to an apical expression of the Na^+-driven Cl^-/HCO_3^- exchanger NDCBE (Fig. 6)(365). The driving force for this transport is provided by the basolaterally localized H^+-ATPase, whereas Cl^- leaves the cell via $CLC_{KB,}$ (365). There is ample evidence that OXGR1 receptor-deficient mice have reduced Na^+ and Cl^- reabsorption (674) and thus, that this pathway is likely to be involved in the overall NaCl homeostasis. However, it must be noted that with the proposed stoichiometry for NDCBE (Fig. 6), the involved transporters cannot provide HCO_3^- secretion and NaCl reabsorption at the same time. This may either suggest that there is a local switch for the NDCBE function allowing differentiation between HCO_3^- secretion and NaCl absorption or the stoichiometry for the NDCBE-like function in intercalated cells is not 2:1:1. In this context, it must be noted that NDCBE to date has not been localized to either CNT or CD by immunohistochemistry even though convincing immunolocalization has been shown for NDCBE in hippocampal slices (87).

In summary, the tubular lumen can be viewed as a conveyer belt for the transport of paracrine factors from a proximal release site to a more distally localized cell and its luminal receptor. The α-KG/ OXGR1 system appears as a powerful paracrine signaling pathway in the kidney for keeping acid/base homeostasis. Interestingly, OXGR1/GPR99 was once inappropriately suggested to be a $P2Y_{15}$ receptor (3), but aside from that, there are practically no studies on the interaction between α-KG/ OXGR1 system and other intrarenal signaling systems. As autocrine/paracrine signaling has an immense influence on pH homeostasis in a variety of cells, one could anticipate that there are interesting novelties to be discovered in that intersection. The α-KG/ OXGR1 system is thus, very unique and does not comply to the overall scheme of paracrine factors in general acting as reno-protective inhibitors of tubular transport.

4. Paracrine signaling in the healthy renal interstitium

Other potential interaction partners for the vascular and epithelial cells are the cells in the interstitial compartment. Most of the studies on the renal interstitial function relate to the development of fibrosis, which we regard as a pathological process, and thus, out of the scope for this review. One can argue that fibrosis is a physiological function of aging. Therefore, our choice to exclude tissue fibrosis is easily challenged. Nonetheless, we here focus on the interstitial function in supporting renal function of the healthy, non-fibrotic kidney. In the healthy kidney, the renal interstitial cells are important to maintain a normal matrix and thus, literately framing the normal renal function. For the renal medulla, this includes producing a high amount of hyaluronan unique for this area of the kidney and which has been suggested to be functionally relevant for urinary concentration (for review see (328, 638)). Below, we will shortly address the interstitial cells as a paracrine signaling partner for the vascular and the epithelial kidney.

Interstitial cells as source of paracrine factors

Interstitial cells may act as a donor of paracrine signaling molecules. As mentioned, the medullary intestinal cell is one of the key cell types that express COX_2 and, thus, a potential source of prostaglandin formation. In addition to the upregulation of COX2 under various pathophysiological states, COX2 expression is increased in the medullary interstitial cells under hypertonic conditions (232), and is reduced under hypotonicity as seen after treatment with furosemide (83). Importantly, the latter study also provided evidence that the down-regulation of COX-expression actually resulted in reduced PGE_2

levels in the renal medulla (83). COX_2 has also been shown to be upregulated in the inner medulla in rats on a high salt diet (86), an effect that is likely also to include the COX level in the intestinal cells. This would result in increased PGE_2 availability for mTAL and IMCD, reinforcing the overall diuresis in response to hypotonicity in the renal medulla and vice versa during antidiuresis. This notion is supported by data showing that COX_2 is upregulated in the medullary interstitial cells in response to AVP (759), which will increase the medullary osmolarity as a function of increased NKCC2 activity in TAL and urea permeability in distal CD.

Regarding the other signaling molecules, there is very little evidence of production and release from renal interstitial cells. Interestingly, CD_{73} or the ecto-5'-nucleotidase that degrades extracellular AMP to adenosine is highly expressed on intestinal fibroblasts in the cortex (359), which at least suggests that the fibroblasts are responsible for formation of some of the interstitial adenosine. Cultured rat medullary intestinal cells have also been shown to express iNOS (NOS2) in low amounts, and the expression was induced by for example TNFα (357), and thus, the interstitial cells are unlikely to be a major source of NO in the uninflamed kidney but may support NO during inflammation/infection.

Responsiveness of interstitial cells to local signaling molecules

The interstitial cells have been demonstrated to have receptors for a wide range of paracrine signaling molecules. This is particularly true for vasoactive peptides. They functionally express angiotensin- receptors, which, as discussed, are essential systemic hormones with important functions in the kidney cannot be regarded as true paracrine signaling molecules in the kidney (771). However, medullary interstitial cells also express receptors for bradykinin (B_2) and endothelin (ET_A, ET_B) (731, 771), which suggest that vasoactive peptides released either form the vasculature or the epithelial cells potentially could impact interstitial cell function. Moreover, stimulation of ET_A has in cultured rat medullary interstitial cells been shown to increase the PGE_2 production (731). Several of the paracrine factors are able to influence the amount of hyaluronan present in the inner medullar and, thus, potentially affect the urinary concentration ability. In cultured rat reno-medullary fibroblasts, endothelin has been demonstrated to have a biphasic effect on hyaluronan production with an ET_B-dependent stimulatory effect in low concentration and an ET_A-dependent inhibition in high concentrations (639). Thus, it is reasonable to assume that ET-1 physiologically will stimulate hyaluronan production and, therefore, support the urinary concentration capacity and not immediately read into the overall renal effect of ET-1. The NO metabolism has also been reported to influence the medullary hyaluronan content. Apparently, inhibition of NO production increases the amount of hyaluronan in the medulla of rats (517), and thus, NO would contribute to a baseline stimulation of hyaluronan production. Collectively there is evidence for direct ET-1 signaling in interstitial cells that supports the overall function of ET-1 on renal function.

Interaction between interstitial cells and vasculature or renal tubules

So is there robust evidence for communication between the interstitial cells and the vasculature or the tubular cells? This is hard to test for specific signaling systems *in vivo*. However, in co-culture, it has been demonstrated that epithelial cells isolated from inner medullary collecting duct cause proliferation of fibroblast isolated from the medulla but not fibroblast isolated from the cortex (327). Whereas this was not the case when co-cultured with epithelial cells isolated from PT (327). Moreover, it has been demonstrated that renal cortical interstitial fibroblasts are stimulated by PT cells in co-culture to increase collagen synthesis and release of insulin-like growth factor I (IGF-1)(296). These studies demonstrate that many renal cell types retain a capacity for interaction and that this intercellular signaling shows some specificity. This is not surprising, and the potential for interaction between the renal interstitial cells and the vascular and tubular structure is exceedingly more extensive than the data highlighted here. Looking into the literature on, for example, less differentiated cultured fibroblasts like the NIH 3T3 cells, basically shows that these cells can release and respond to virtually all the paracrine substances discussed in this review. Therefore, it is reasonable to assume that most of the autocrine/paracrine molecules affecting the vascular and tubular cells will also affect the interstitial cells and vice versa. The essence is, however, to find the functional implications of this interaction, which in terms of physiology currently is limited to ET-1 and PGE_2.

5. Renal autoregulation - an extension of the fundamental concept of self-regulation

Our fascination with all the paracrine factors influencing the renal function often subsides into frustration over how difficult it is to acquire a proper overview of the entire system. We find that it would be exceedingly helpful to be able to be more precise with regard to the function of autocrine/paracrine signaling in the kidney. Here, we propose a framework for paracrine signaling in the kidney as a reference for future work on an integrated understanding of renal physiology. As mentioned in the introduction, we are well aware that we will not be able to highlight all the interesting aspects of local signaling for the benefit of outlining the main trends. We have concentrated on the pivotal task of the kidney, namely the balanced water and electrolyte excretion, and how the established paracrine systems modulate this function. This brings the vascular effect on filtration and the following tubular handling of salt and water into the limelight. For the vascular part, we ask how does a given paracrine factor affect the renal autoregulatory system: the myogenic response and the TGF mechanism. For the tubular system, we consider the specific effect on water and salt handling of each tubular segment and weigh the relative importance of every segment in the light of the collected effect on diuresis and NaCl excretion. By this approach, we have drawn the main lines to ease the navigation when studying the autocrine/paracrine signaling in the kidney.

Renal autoregulation. The renal autoregulation is a regulatory system that allows the kidney to provide steady blood flow and GFR regardless of fluctuation in systemic blood pressure. In that sense, the kidney essentially works autonomously and excrete exactly the water and electrolyte needed to keep body homeostasis. Another consequence of autoregulation is that strict local control of the filtration limits the amount of water and solutes delivered to each nephron, thereby avoids to overburden the functional absorptive capacity of the tubular system. In that sense, self-protection is an intrinsic component of autoregulation, and renal autoregulation itself should be considered a subset of the mechanisms by which the kidney self-regulates. The notion that the renal autoregulation is a self-preservation system is underscored by the renal damage observed in response to the hyperfiltration in the early phases of diabetes mellitus. The classic autoregulation of the kidneys consists of (1) the myogenic response, which

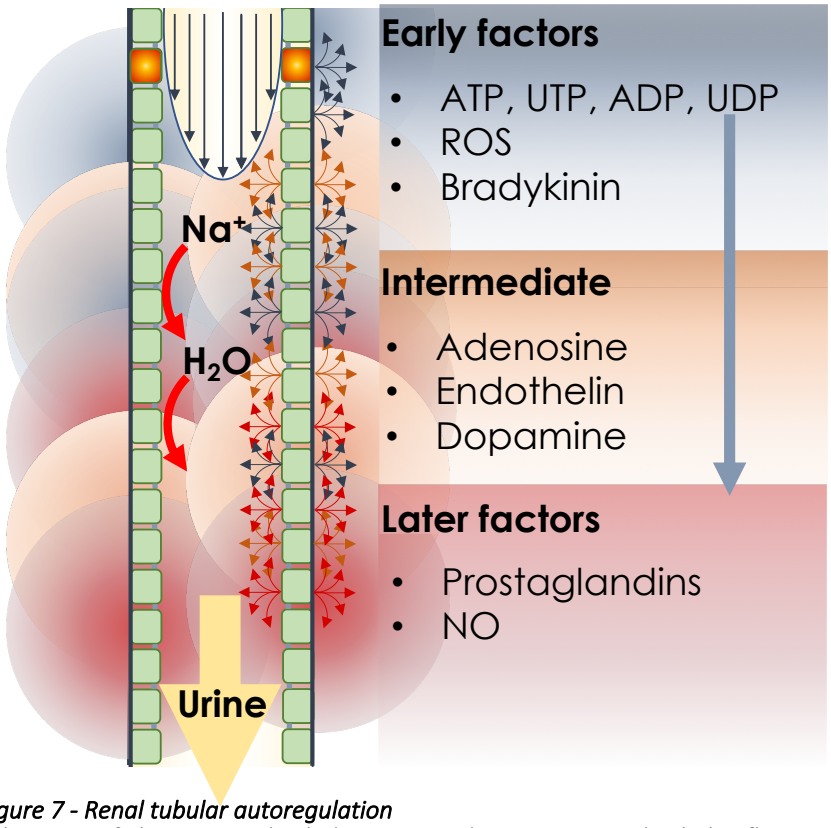

Figure 7 - Renal tubular autoregulation
Schematic of the proposed tubular autoregulation. Increased tubular flow is used as an example of a trigger of paracrine signaling. The release of paracrine factors in the blue category of early release factors occurs in response to the flow-induced activation of the renal epithelial cells. The release of the paracrine factors is illustrated by the arrows of the corresponding color and the cloud surrounding it. The early response factors trigger the release of intermediate, which further stimulates the release of the late factors. The overlapping release clouds create a milieu surrounding the tubule for an integrated tissue response, which is reduced NaCl and water reabsorption and, thus, increased urine output.
Abbreviations: ATP (adenosine triphosphate), ADP (adenosine diphosphate), NO (nitric oxide), ROS (reactive oxygen species), UTP (uridine triphosphate), UDP (uridine diphosphate)

constantly adapts the diameter of the afferent arteriole according to the systemic blood pressure and (2) the TGF mechanism that is activated by an increased filtration and thus, tubular NaCl load (Fig. 2). Paracrine signaling is implicated in both the myogenic and the TGF response, which safeguards the kidney and secures a steady renal function during the physical activity and posture changes.

Apparently, self-regulation of renal blood flow is not only confined to the myogenic response and the TGF mechanism. Several studies indicate functionally important communications between tubular and vascular segments also occurring in other parts of the kidney. The group of Connor and Cowley has worked with the hypothesis that the mTAL affects the blood flow of vasa recta. They were intrigued by the pericytes surrounding the vasa recta (for review see (480)), which have the potential to regulate the medullary blood flow at the capillary level. A paper from 2012 showed that AngII caused a pericyte-dependent narrowing of vasa recta, when these segments were dissected completely free from surrounding tissue and perfused alone (455). Interestingly, this AngII effect was not observed when a thick ascending limb was allowed to stay attached to the vasa recta during perfusion, indicating that NO released from TAL counteract the AngII-induced vasoconstriction (455). This report not only suggests paracrine interaction between tubular segments and vasculature in the kidney but underscores that the renal autoregulation can dampen the effect of systemic hormones. Thus, the overall renal effect of any systemic hormone can only be understood in the context of local paracrine signaling.

Is the tubular function self-regulated?

The concept of autoregulation has, thus far, either been described as a function confined to the vasculature in the case of the myogenic response or as an interaction between the tubular system and the vasculature. However, could the basic principle of self-regulation be applied more broadly as renal self-protection, and be used for confined tubular effects as well?

As mentioned, self-preservation is implicit in the term autoregulation and is a fundamental principle for any organ to preserve its function, from the level of the tissue's functional units down to the single-cell components. A cells specific task or workload is always to be precisely matched to the available energy and, thus, to the substrate and oxygen supply. Sustaining a high epithelial transport rate is a continuous energetic, and homeostatic challenge for the epithelial cells. In the case of an absorbing renal epithelial cell, the reabsorption-process can never feast on the energy needed to keep the cell's housekeeping. If this happens, cell survival and thus, kidney function would be threatened. Therefore, a reabsorbing cell must have an inbuilt mechanism to shut down or limit transport, when stressed or overburdened. Here, we propose that a web of paracrine factors entail a local self-regulatory system that is able to uncouple the reabsorptive process in the tubules when the renal epithelial cell function is jeopardized.

Keeping the helicopter perspective on paracrine signaling in renal tubules, it is striking that the majority of the paracrine factors inhibit tubular transport. Table 2 provides a summary of all the

Effect of paracrine factors on epithelial transport

Paracrine factors	Inhibition	Stimulation	Reference
Adenine	+		(321)
Adenosine	+	+ (PT)	Act (PT):124, 160, 345, 722 Inh (TAL, CDT, CD): 35, 141, 304, 361, 490, 697, 718, 741, 744
α-ketogluterat		+	358, 674
ATP/UTP	+++		23 ,103, 318, 362, 401,550, 603, 645, 662, 730, 764
Bradykinin	+++		31, 250, 426, 572,610, 611, 634, 654, 679, 680, 732, 755, 758,
Dopamine	+++		17, 27, 117, 156, 157, 214, 215, 269, 292, 494, 714
Endothelin	+++		22, 69, 143, 181, 189, 206, 225, 348, 461, 574, 678, 757
HETEs	+++		152, 153, 172, 287, 450, 464, 489, 536, 605, 708,
H_2O_2		+	606
Nitrc oxide	+	+ (PT)	Act: 55, 56, 381, 635, 636, 709, 710 Inh: 144, 192, 226, 373, 449, 469, 492, 504, 505, 544, 635, 636, 736
O_2^-		++	299, 398, 399 470, 472, 557, 752, 773
Prostaglandines	+++	+ (PT)	Act: 127, 252, 462, 566, 568, 569, inh: 54, 104,105, 161, 209, 247, 249, 303, 552, 631, 632
Renin/prorenin		++	385, 519

Table 2

discussed paracrine factors and their overall effect on transepithelial transport. The table shows that a paracrine factor is an exception to the rule if it stimulates epithelial transport. Thus, it is a tempting thought that all these single factors collectedly are indeed able to protect the renal tubules against overstimulation. The local release of the majority of the paracrine factors will as long as they are present in the surrounding extracellular space, reduce the transport, and allow the cell to recuperate from a potentially stressful situation. This is illustrated by several examples that support the notion that increased tubular transport renders the cells more susceptible to damage, whereas reduction of transport protects them. This principle is, for example, illustrated by the inhibition of PT transport by dopamine, and that mice with high PT dopamine levels are protected against renal damage, whereas the opposite is true for mice lacking PT dopamine production.

Interdigitation between renal paracrine factors

Interrelations	References
ATP triggers NO formation in the mTAL	74
Endothelin-1 increases NO formation in TAL and IMCD	637, 115, 503
ATP stimulates Endothelin production and release	485
Bradykinin increases NO production in the vasculature - and in renal epithelial cells	235, 353
Bradykinin triggers PG release	410, 585
Bradykinin triggers pro-renin abundance and mRNA in CD	353
ATP causes PGE_2 release from isolated IMCD	721
Endothelin can trigger PGE_2 release in the IMCD	334
Dopamine stimulates PGE_2 release from IMCD cells	271

Table 3

Paracrine signaling is activated when there is an increased strain on the renal cells. The trigger mechanism includes mechanical stress, osmotic challenge, or, in some instances, hormonal stimulation. The triggering signals are illustrated, for example, by ATP release in response to minuscule deflection of primary cilia or microvilli (for review see (512, 513)). This type of minor stress to a single cell will then via recruitment of a cascade of the local signaling systems develop into a coordinated tissue response that protects the epithelium (Fig. 7).

Another important aspect is that all the paracrine factors have effective degradation systems. This means that the renal protection is self-limited if the initial threat disappears. If this was not the case, constant activation of the autocrine/paracrine signaling factors could potentially lead to renal salt and water wasting and thereby prevent the kidneys from serving their true purpose of keeping the overall body homeostasis. Thus, it is a beautiful trade of the renal autocrine/paracrine signaling system that it rapidly can be called upon during renal stress and then return to baseline levels when the situation is normalized.

A web of paracrine factors governs the renal function

The large number of paracrine factors listed in table 2 immediately trigger the questions like 'Why so many?' and –'Which one is the most important?' Our typical answer to why various factors inflict a similar response is usually redundancy, which essentially means that the systems can substitute for one another. Interestingly, each of the paracrine systems has its own flavor. Some are released instantly and degraded immediately after the initial stimulus, while others such as adenosine are degradation products, and thus, enters the scene with a little delay, which potentially could sustain the effect long enough to ensure a coordinated tissue response. Other factors like endothelin are able to prolong effect further because they keep on working even after the agonist-receptor complex is internalized into the cell. Therefore, it is not meaningful to ask which of the paracrine factors is the most important one. But it does make sense to categorize the paracrine factors in terms of the overall kinetics – that is to define when they come into play and which other factors they call upon to modulate the effect.

A key feature of paracrine signaling is that many of the paracrine factors are able to mediate the release of other paracrine factors. Some of these examples are summarized in table 3, including NO release in response to endothelin-mediated ET_B receptor activation and endothelin release in response to purinergic signaling. These multiple interactions make us propose the term *web of paracrine factors*, which essentially means that paracrine factors, in general, can call upon each

other for an integrated and coordinated tissue response. Figure 7 illustrates the principle of the paracrine web. It shows an initial response that liberates a fast, transient paracrine molecule (blue), which mobilizes other paracrine factors (orange and/or red) for further amplification and coordination of the whole tissue response. We propose an organization of the factors in three groups: (1) a group of early factors, released immediately after the initial mechanical stimulus, e.g., ATP, (2) an intermediate group released in response to the early factors e.g., endothelin and (3) a late group that is released in response to either of the previously released factors, e.g., prostaglandins. The final effect is an inhibition of epithelial transport that leaves Na^+ and water in the tubular lumen creating the diuresis and natriuresis, which is the common overall effect of the majority of the paracrine factors. **We propose that the tubular paracrine signaling is synonymous with the renal self-regulation. When perturbed, the kidney releases a web of paracrine signaling molecules that collectively reduce tubular reabsorption until the given threat has succumbed**.

5. Conclusion and perspective

The survey of the field has led us to the bold conclusion that renal paracrine signaling and renal self-regulation are two sides of the same coin. We have outlined the fundamental principle that the intrarenal paracrine systems weave a safety net for the kidney protecting against it being overburdened by external stimuli.

Looking at autocrine/paracrine signaling collectively as a reno-protective system has vast scientific and clinical perspectives. Renal insufficiency is one of the leading challenges for the health systems worldwide, and the capacity for renal transplantation cannot meet the needs. We are born with a finite number of functioning nephrons that steadily declines with advancing age, and the rate of decline is accelerated by various lifestyle risk factors and chronic diseases. Thus, there is a keen interest in defining renal protective factors and regimes to postpone the date for running into renal insufficiency. We firmly believe that some of the answers can be found in supporting the kidney's own line of defense and, thus, in the renal autoregulation seen as a sum of autocrine/paracrine signaling mechanisms. This notion is emphasized by the reno-protective effect of SGLT-2 inhibition shown both in clinical studies and by real-world data. We mentioned the hyperfiltration seen in early phases of diabetes mellitus as an example of the renal damages that occurs when the kidney is constantly overburdened. On the same note, SGLT-2 inhibition in the treatment of DM is known to relieve the kidneys from hyperfiltration, most likely by modifying intrarenal autocrine/paracrine signaling and autoregulation. This illustrates the potential in promoting the inert reno-protective mechanisms to bent the curve of progression towards renal insufficiency.

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